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(71) Applicants *(for all designated States except US)*: **DANA-FARBER CANCER INSTITUTE, INC.** [US/US]; 44 Binney Street, Boston, MA 02115 (US). **TRUSTEES OF BOSTON UNIVERSITY** [US/US]; 147 Bay State Road, Boston, MA 02215 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **SCHULTZE, Joachim, L.** [DE/US]; 37 Auburn Street, Brookline, MA 02146 (US). **VONDERHEIDE, Robert, H.** [DE/US]; Apartment 801, 1284 Beacon Street, Brookline, MA 02115 (US). **SHERR, David** [US/US]; 39 Hastings Street, West Roxbury, MA 02132 (US). **NADLER, Lee, M.** [US/US]; 36 Cross Hill Road, Newton, MA 02159 (US). **MAECKER, Britta** [DE/US]; 368 Longwood Avenue, #21, Boston, MA 02215 (US). **VON BERGWELT-BAILDON, Michael** [DE/US]; 24 A Prentiss Street, Cambridge, MA 02140 (US).

(74) Agent: **CLARK, Paul, T.**; Clark & Elbing LLP, 176 Federal Street, Boston, MA 02110-2214 (US).

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(54) Title: CANCER IMMUNOTHERAPY AND DIAGNOSIS USING CYTOCHROME P450 1B1

(57) Abstract: The invention provides methods for conducting cancer immunotherapy and diagnosis using cytochrome P450 1B1 and peptide fragments thereof.

CANCER IMMUNOTHERAPY AND DIAGNOSIS USING CYTOCHROME P450 1B1

Background of the Invention

This invention relates to the prevention, treatment, and diagnosis of cancer.

The paucity of clinically significant anti-tumor immune responses in cancer patients has long suggested that antigen-specific immunotherapy would not play a significant role in cancer treatment. However, pioneering studies in the early 1990s, using tumor-specific cytotoxic T lymphocytes (CTLs) from cancer patients, showed the existence of human tumor associated antigens (TAAs). This led to the suggestion that such antigens could be used to stimulate therapeutic anti-tumor immune responses in patients. Although these studies focused primarily on melanoma, TAAs have also been characterized in several other malignancies (Van Pel *et al.*, Immunological Reviews 145:229-250, 1995; Rosenberg, Immunol. Today 18:175-182, 1997; Van den Eynde *et al.*, Curr. Opin. Immunol. 9:684-693, 1997), raising the hypothesis that most, if not all, tumors express antigens that can be used to induce CTL-mediated tumor destruction. Consequently, clinical efforts are now underway to target TAAs in strategies, such as vaccination and adoptive T cell therapy, to generate effective anti-tumor CTL responses in patients.

The demonstration that TAA-specific immune responses can lead to tumor regression has been borne out extensively in animal models (Rosenberg, Immunity 10:281-287, 1999). Although the identification of TAAs using patients' CTLs has revitalized the field of T cell immunotherapy, these methods are slow, very expensive, and labor-intensive. Moreover, the strategy relies on the generation of tumor-specific T cell clones *in vitro*, suggesting that only a restricted set of TAAs will be identified by this method. With these limitations in mind, Pfreundschuh and colleagues developed an alternative approach, SEREX

(serological identification of antigens by recombinant expression cloning), to identify TAAs (Sahin *et al.*, Curr. Opin. Immunol. 9:709-716, 1997). SEREX makes use of patients' antibody responses to tumor-derived genes and this strategy has accelerated the identification of TAAs significantly. Although several T cell-defined TAAs, such as the MAGE genes, have also been identified by SEREX, there is no information available about CTL epitopes for the vast majority of genes in the SEREX database, and, of course, such epitopes are required to activate a CTL response.

Although there is no doubt that the identification of numerous TAAs by CTL-based approaches or SEREX reflects the existence of an anti-tumor immune response, it remains to be determined if these antigens play a role as tumor regression antigens (Sarma *et al.*, J. Exp. Med. 189:811-820, 1999). Indeed, most T cell epitopes in TAAs identified by patient CTLs have been demonstrated to be of low MHC binding affinity and/or low MHC/peptide complex stability. This quality distinguishes TAA-derived peptides from viral peptides that are almost exclusively of high binding affinity and high MHC/peptide complex stability (Feltkamp *et al.*, Mol. Immunol. 31:1391-1401, 1994; Sette *et al.*, J. Immunol. 153:5586-5592, 1994). Clinical vaccination trials have circumvented this obstacle by utilizing altered peptides with higher MHC binding affinity and higher MHC/peptide complex stability (Rosenberg *et al.*, Nat. Med. 4:321-327, 1998). The low binding affinity of TAA-derived peptides is likely to be one of the reasons why natural CTL responses against such peptides are not successful for tumor eradication. This is in agreement with the finding that large numbers of TAA-specific CTLs co-exist with metastatic tumors in melanoma patients (Romero *et al.*, J. Exp. Med. 188:1641-1650, 1998). A recent study has even demonstrated that despite expansion, such CTLs were hyporesponsive, showing reduced cytotoxic and cytokine responses (Lee *et al.*, Nat. Med. 5:677-685, 1999).

In addition, most TAAs described thus far are expressed in only one or a few tumor types, and not all patients with a given tumor type express the associated TAA. As a result, progress in the field of cancer immunotherapy has been relatively slow, because it has not been possible to develop widely useful

TAA-specific immunotherapeutic strategies. Not only has it been necessary to tailor such therapies to individual types of malignancies, in some cases (such as the immunoglobulin idiotypic antigen in B cell malignancies), it has been necessary to tailor these therapies to individual patients.

Summary of the Invention

The invention provides a method of treating a patient that has or is at risk of having a cell that expresses cytochrome P450 1B1 (CYP1B1). This method involves administering to the patient a cytotoxic T lymphocyte (CTL)(autologous or allogeneic) that leads to death of (from here on said as kill) the cell in a CYP1B1-specific, major histocompatibility complex-restricted fashion. The CTL can be generated, for example, by activation with an antigen presenting cell that has been pulsed with CYP1B1, or a peptide of CYP1B1 that binds to a major histocompatibility complex molecule.

The invention also includes a second method of treating a patient that has or is at risk of having a cell that expresses CYP1B1. This method involves administering to the patient an antigen presenting cell (APC) that activates in the patient a cytotoxic T lymphocyte that kills the cell in a CYP1B1-specific, major histocompatibility complex-restricted fashion. The APC can be pulsed with CYP1B1 or a peptide of CYP1B1 that binds to a major histocompatibility complex molecule.

Another method included in the invention is a third method of treating a patient that has or is at risk of having a cell that expresses CYP1B1. This method involves administering to the patient CYP1B1 or a peptide of CYP1B1 that binds to a major histocompatibility complex molecule, which is processed by an antigen presenting cell in the patient, which, in turn, activates a cytotoxic T lymphocyte in the patient to induce cell death of the cell that expresses CYP1B1 in a CYP1B1-specific, major histocompatibility complex-restricted fashion. The CYP1B1 polypeptide or peptide of CYP1B1 used in this method can be administered to the patient in association with an adjuvant.

The invention also includes a fourth method of treating a patient that has or is at risk of having a cell that expresses CYP1B1. This method involves administering to the patient a nucleic acid molecule encoding CYP1B1 or a peptide of CYP1B1 that binds to a major histocompatibility complex molecule. The nucleic acid molecule is expressed in the patient so that it can be processed by an antigen presenting cell in the patient, which activates a cytotoxic T lymphocyte in the patient to induce cell death of the cell that expresses CYP1B1, in a CYP1B1-specific, major histocompatibility complex-restricted fashion. The nucleic acid molecule encoding CYP1B1 or a peptide of CYP1B1 can be present in an expression vector.

Each of the methods described above can also include treatment based around a second (or more) tumor associated antigen, *e.g.*, telomerase (hTERT, PCT/US99/25438), or a peptide thereof that binds to MHC (*e.g.*, the I540 peptide).

In any of the methods described above, the patient can have a tumor containing cells that express CYP1B1. APCs used in these methods can be, for example, a dendritic cell or a CD40-activated B cell. The peptide of CYP1B1 in these methods can bind to a class I or a class II major histocompatibility complex (MHC) molecule. In the case of a class I MHC molecule, the molecule can be, for example, an HLA-A2 molecule, and the peptide of CYP1B1 can include the amino acid sequence of CYP239 (SEQ ID NO:1; SLVDVMPWL), CYP246 (SEQ ID NO:2; WLQYFPNPI), CYP190 (SEQ ID NO:3; FLDPRPLTV), or CYP528 (SEQ ID NO:4; LLDSAVQNL). Examples of other CYP1B1 sequences that can be used in these methods are set forth in the Sequence Appendix and in Tables 3-10.

The invention also includes a method of assessing the level of immunity of a patient to CYP1B1 or a peptide of CYP1B1 that binds to a major histocompatibility complex molecule. In this method, the level of cytotoxic T lymphocytes specific for CYP1B1 or a peptide of CYP1B1 is measured in a sample from a patient. The sample can be obtained from the patient before,

during, or after a cancer treatment is administered to the patient. A sample can also be obtained, for example, before and after treatment.

The invention also includes CYP1B1 peptides that bind to major histocompatibility complex molecules, for example, a peptide that consists essentially of the amino acid sequence set forth in SEQ ID NO:1 (CYP239), SEQ ID NO:2 (CYP246), SEQ ID NO:3 (CYP190), or SEQ ID NO:4 (CYP528).

Also included in the invention is an *ex vivo* generated cytotoxic T lymphocyte that specifically kills a cell expressing CYP1B1 in a specific, major histocompatibility complex-restricted fashion, and an *ex vivo* generated antigen presenting cell (*e.g.*, a dendritic cell or a CD40-activated B cell) that presents a peptide of CYP1B1 in the context of a major histocompatibility complex molecule.

As is understood in the art, a "polypeptide" is a chain of amino acids linked to one another by peptide bonds. A "protein" can be made up of one or more polypeptides, while a "peptide" is generally understood to be (or include) a fragment of a polypeptide, and to consist of a chain of peptide bond-linked amino acids that is shorter in length than a full length polypeptide from which it may be derived.

A "tumor associated antigen," such as CYP1B1, is an immunogenic molecule, such as a protein, that is, generally, expressed at a higher level in tumor cells than in non-tumor cells, in which, preferably, it may not be expressed at all, or only at low levels. A tumor associated antigen, or TAA, is said to be "universal" if it is expressed in tumors of different origins.

A "cytochrome P450 1B1 polypeptide," or a "CYP1B1 polypeptide" is a full length, non-fragmented polypeptide of CYP1B1, while a "cytochrome P450 1B1 peptide," or a "CYP1B1 peptide," is (or includes) a fragment of such a CYP1B1 polypeptide. CYP1B1 peptides can be of any length, up to just under the full length of a CYP1B1 polypeptide. However, preferably, for use in the invention, CYP1B1 peptides are of a relatively short length, such as, for example, eight, nine, ten, eleven, or twelve amino acids. Also, a CYP1B1 peptide may include sequences that are not present in a corresponding CYP1B1 polypeptide,

provided that the CYP1B1 peptide also includes a stretch of at least, for example, eight, nine, ten, eleven, or twelve consecutive amino acids that have a sequence that is identical to a sequence of eight, nine, ten, eleven, or twelve consecutive amino acids in a CYP1B1 polypeptide.

Peptides including amino acid substitutions can also be considered as CYP1B1 peptides. For example, a CYP1B1 peptide can include a region of at least nine amino acids, of which any six or more are identical to the amino acids within a nine amino acid stretch in CYP1B1. Preferably, at least seven, more preferably, at least eight, and, most preferably, all nine of the amino acids in a CYP1B1 peptide nine amino acid region are identical to a nine amino acid region in the CYP1B1.

A CYP1B1 polypeptide corresponding to CYP1B1 includes 533 amino acids that are substantially identical (see below) to the amino acid sequence of CYP1B1 (Sutter *et al.*, J. Biol. Chem. 269:13092-13099, 1994; Tang *et al.*, J. Biol. Chem. 271:28324-28330, 1996; Genbank Accession No. U56438), or such a polypeptide can include the amino acid sequence of CYP1B1, as well as additional sequences.

As is discussed further below, it is preferable that CYP1B1 polypeptides of the invention include regions that bind to major histocompatibility complex (MHC) antigens. Preferred examples of CYP1B1 peptides that are included in the invention are CYP239 (SEQ ID NO:1), CYP246 (SEQ ID NO:2), CYP190 (SEQ ID NO:3), and CYP528 (SEQ ID NO:4). Additional CYP1B1 peptides are listed in the Sequence Appendix, as well in Tables 3-10, and still more CYP1B1 peptides can be identified using methods described below (also see PCT/US99/25438).

A CYP1B1 peptide or polypeptide can be fused to amino acid sequences that do not naturally occur in CYP1B1. Moreover, a CYP1B1 peptide or polypeptide can be attached to the surface of a cell or to a molecule or a macromolecule (*e.g.*, a histocompatibility antigen), or a CYP1B1 peptide or polypeptide can be conjugated to immunogens or adjuvants that are known to those of skill in this art, for example, keyhole limpet hemocyanin (KLH), for the

purpose of eliciting a CYP1B1-specific immune response. As is noted above, preferred examples of CYP1B1 peptides are CYP239 (SEQ ID NO:1), CYP246 (SEQ ID NO:2), CYP190 (SEQ ID NO:3), and CYP528 (SEQ ID NO:4).

By "CYP1B1 nucleic acid molecule" is meant a DNA or RNA (*e.g.*, mRNA) molecule that encodes a CYP1B1 polypeptide or CYP1B1 peptide, as are defined above.

By "CYP1B1-expressing tumor cell" is meant a tumor cell that expresses CYP1B1. A CYP1B1-expressing tumor cell can express a level of CYP1B1 that is equal to, or, preferably, greater than the level of CYP1B1 expressed by the normal cell type from which the CYP1B1-expressing tumor cell has originated, or other non-tumor cells. Preferably, the tumor cell expresses at least 10% more CYP1B1, more preferably, at least 25% more, still more preferably at least 50% more, and most preferably at least 150% more CYP1B1 than the normal cell type from which the CYP1B1-expressing tumor cell has originated, or another non-tumor cell. CYP1B1 expression levels in a CYP1B1-expressing tumor cell can be increased by, for example, increased transcription of the CYP1B1 gene, increased CYP1B1 mRNA stability or translation, increased CYP1B1 polypeptide stability, or increased CYP1B1 enzymatic activity. Increasing such CYP1B1 expression levels may be useful in the invention to increase the likelihood that a tumor cell will be recognized as a target of the immunotherapeutic methods described herein (see below).

By "histocompatibility antigen" is meant a molecule, such as a major histocompatibility complex (MHC) class I, MHC class II, or minor histocompatibility antigen, that mediates interactions of cells of the immune system with each other and with other cell types. Examples of histocompatibility antigens include MHC class I antigens, such as HLA-A (*e.g.*, A1, A2, A3, A11, A24, A31, A33, and A38), HLA-B, and HLA-C, MHC class II antigens, such as HLA-DR, HLA-DQ, HLA-DX, HLA-DO, HLA-DZ, and HLA-DP, and minor histocompatibility antigens, such as HA-1.

By "generating CTLs" is meant an *in vivo*, *in vitro*, or *ex vivo* process by which CTLs (*e.g.*, CYP1B1-specific CTLs) are activated (*e.g.*, stimulated to grow and divide) and/or selected.

A peptide of CYP1B1 is said to "specifically bind" to an MHC antigen if the peptide adheres to a histocompatibility antigen under physiological conditions. For example, such binding can be similar to that of a peptide antigen that is naturally processed and presented in the context of MHC in an antigen presenting cell.

A cytotoxic T lymphocyte (CTL) or antibody is said to "specifically recognize" a CYP1B1 polypeptide or a CYP1B1 peptide if it binds to the polypeptide or peptide, but does not substantially bind to other, unrelated polypeptides or peptides.

A CTL is said to "specifically kill" a cell if it specifically recognizes and lyses a cell that expresses an antigen (*e.g.*, CYP1B1) to which it has been activated, but does not substantially recognize or lyse cells not expressing the antigen. In the case of CYP1B1, such a CTL is designated as a "CYP1B1-specific CTL" herein.

By "CYP1B1-specific antibody" is meant an antibody that can specifically recognize and bind to a CYP1B1 peptide or polypeptide, and that does not substantially recognize and bind to other, unrelated molecules.

A CYP1B1 polypeptide is "presented" if a peptide of CYP1B1 is displayed on the extracellular surface of a cell (*e.g.*, an antigen presenting cell), such that it can result in the *in vivo*, *ex vivo*, or *in vitro* generation of CYP1B1-specific CTLs or the lysis of a tumor cell by a CYP1B1-specific CTL. Preferably, the displayed CYP1B1 peptide is bound to a histocompatibility antigen.

By "physiological conditions" is meant the *in vivo* environment in which CYP1B1-specific CTLs are generated (activated and/or selected) and perform their biological functions (*e.g.*, recognition of a CYP1B1 peptide and MHC-restricted lysis of CYP1B1-expressing tumor cells), or an *in vitro* or *ex vivo* environment that allows CYP1B1-specific CTLs to be generated and to perform their biological functions.

By "CYP1B1 vaccination" is meant administration of an immunogenic preparation including one or more CYP1B1 peptides, CYP1B1 polypeptides, CYP1B1 nucleic acid molecules, fragments of any of these molecules, CYP1B1-presenting cells (*e.g.*, dendritic cells or CD40-activated B cells), or mixtures thereof. Vaccination is performed on a subject who has a tumor, has a history of having a tumor or tumors, is likely to develop a tumor, or any healthy individual to prevent tumors, or on a subject in which CYP1B1-specific immune cells (such as CTLs) are to be generated for transfer into a patient. Such vaccination stimulates a CYP1B1-specific immune response within the subject. In subjects having tumors, the vaccination can result in partial or complete inhibition of tumor growth, or partial or complete tumor regression, provided that the patient's tumor expresses CYP1B1. In addition, vaccination can provide prophylaxis against the development of new CYP1B1-expressing tumors.

A "vaccine," as used herein, is an immunogenic composition that can be administered in the vaccination method described above. Thus, a vaccine includes, for example, one or more CYP1B1 peptides, CYP1B1 polypeptides, CYP1B1 nucleic acid molecules, fragments of any of these molecules, CYP1B1-presenting cells (*e.g.*, dendritic cells or CD40-activated B cells), or mixtures thereof. Optionally, a vaccine composition can also include an adjuvant, which is a molecule that stimulates an immune response to a co-administered vaccine antigen. Examples of adjuvants that can be used in the invention are provided below. A vaccine composition can also include other tumor associated antigens (*e.g.*, hTERT) or peptides thereof (PCT/US99/25438).

By "immune cell" is meant any cell that plays a role in cell-mediated or humoral immunity, including CTLs and antigen-presenting cells, *e.g.*, B cells, T helper cells, and dendritic cells.

By "sample" is meant a tumor or tissue biopsy, a lymph node biopsy, bone marrow, cells, blood, serum, urine, stool, sputum, saliva, or other specimen obtained from a patient. A sample can be analyzed to determine the level of CYP1B1-specific CTLs, the level of CYP1B1-specific antibodies, or the level of any other immune response indicator (*e.g.*, a cytokine) in the patient from whom

it was taken by methods that are known in the art. For example, ELISA can be used to measure levels of CYP1B1-specific antibodies, and ELISPOT can be used to measure cytokine levels. Also, Cr^{51} release (T cell cytotoxicity) assays and assays that test the binding of CTLs to tetrameric CYP1B1 peptide/MHC complexes, as described herein, can be used to measure levels of CYP1B1-specific CTLs.

By "reference sample" is meant a sample in which the level of CYP1B1-specific CTLs or the level of CYP1B1-specific antibodies have been measured, and to which the level of CYP1B1-specific CTLs or the level of CYP1B1-specific antibodies in a test subject's sample are compared. Reference levels can be higher, lower, or the same as patient sample levels. Comparison of a test sample to a reference sample provides an assessment of the CYP1B1-specific immune response in the test subject. In addition, comparison of a patient's sample levels to reference sample levels can allow a diagnosis of cancer and/or a prognosis of a cancer in a patient having a tumor that includes CYP1B1-expressing cells.

By "cancer treatment" is meant any therapy (*e.g.*, chemotherapy, radiation therapy, administration of a tumor associated antigen (*e.g.*, CYP1B1)-specific CTLs, administration of an APC presenting a peptide of a TAA (*e.g.*, CYP1B1), or vaccination with a TAA (*e.g.*, CYP1B1), a nucleic acid molecule encoding a TAA (*e.g.*, CYP1B1), or a fragment thereof, to enhance an anti-tumor immune response) administered either alone or in combination with other therapies, that alleviates disease in at least some patients to which the treatment is administered. For example, a cancer treatment can reduce or inhibit tumor growth, or can induce partial or complete tumor regression. Furthermore, a cancer treatment can be prophylactic, in that it inhibits or prevents the development of new tumors in healthy individuals, in patients that are in remission from cancer, have metastatic cancer, or have a high risk of developing cancer.

By "inhibiting the development of a tumor" is meant administering a protective therapy (such as CYP1B1-specific CTLs, CYP1B1 peptide presenting APCs, or a vaccine including, for example, one or more CYP1B1 peptides, CYP1B1 polypeptides, or CYP1B1 nucleic acid molecules, or a combination thereof) to a subject adjudged to have a higher than average risk of developing a tumor. Subjects with a relatively high risk of developing a tumor include those having a family history of cancer, those having one or more genetic mutations that are associated with a high risk for cancer (*e.g.*, a mutation that inactivates a tumor suppressor gene), those having relatively high levels of CYP1B1-specific CTLs or CYP1B1-specific antibodies, those who have cancer or are in remission from cancer, and those who have been exposed to agents known or suspected to cause cancer.

By "pharmaceutically acceptable carrier" is meant a carrier that is physiologically acceptable to a treated patient, while retaining the therapeutic properties of the compound with which it is administered. One exemplary pharmaceutically acceptable carrier is physiological saline. Other physiologically acceptable carriers and their formulations are known to those skilled in the art, and are described, for example, in *Remington's Pharmaceutical Sciences* (18^{th} edition), ed. A. Gennaro, 1990, Mack Publishing Company, Easton, PA.

The term "substantially identical" is used herein to describe a polypeptide or nucleic acid molecule exhibiting at least 50%, preferably at least 85%, more preferably at least 90%, and most preferably at least 95% identity to a reference amino acid or nucleic acid sequence. For polypeptides, the length of comparison sequences is at least 8 amino acids, preferably at least 16 amino acids, more preferably at least 25 amino acids, and most preferably 35 amino acids. For nucleic acid molecules, the length of comparison sequences is at least 24 nucleotides, preferably at least 50 nucleotides, more preferably at least 75 nucleotides, and most preferably at least 110 nucleotides. Sequence identity is typically measured using sequence analysis software with the default parameters specified therein (*e.g.*, Sequence Analysis Software Package of the Genetics Computer Group, University of Wisconsin Biotechnology Center, 1710

University Avenue, Madison, WI 53705). The CYP1B1 polypeptides, peptides, and nucleic acid molecules of the invention can be identical or substantially identical to naturally occurring molecules, and thus may or may not include non-wild type sequences.

By "substantially pure peptide" or "substantially pure polypeptide" is meant a peptide, polypeptide, or a fragment thereof, which has been separated from the components that naturally accompany it. Typically, the peptide or polypeptide is substantially pure when it is at least 60%, by weight, free from the proteins and naturally-occurring organic molecules with which it is naturally associated. Preferably, the peptide or polypeptide is a CYP1B1 peptide or polypeptide that is at least 75%, more preferably at least 90%, and most preferably at least 99%, by weight, pure. A substantially pure CYP1B1 peptide or polypeptide can be obtained, for example, by extraction from a natural source (*e.g.*, a tumor cell), by expression of a recombinant nucleic acid molecule encoding a CYP1B1 peptide or polypeptide, or by chemically synthesizing the peptide or polypeptide. Purity can be measured by any appropriate method, *e.g.*, by column chromatography, polyacrylamide gel electrophoresis, or HPLC analysis.

A protein is substantially free of naturally associated components when it is separated from those contaminants that accompany it in its natural state. Thus, a protein that is chemically synthesized or produced in a cellular system different from the cell from which it naturally originates is substantially free from its naturally associated components. Accordingly, substantially pure peptides and polypeptides not only include those derived from eukaryotic organisms, but also those synthesized in *E. coli* or other prokaryotes.

By "substantially pure DNA" or "isolated DNA" is meant DNA that is free of the genes that, in the naturally-occurring genome of the organism from which the DNA is derived, flank the gene. The term thus includes, for example, a recombinant DNA that is incorporated into a vector; an autonomously replicating plasmid or virus; or the genomic DNA of a prokaryote or eukaryote; or DNA that exists as a separate molecule (*e.g.*, a cDNA, or a genomic or cDNA fragment

produced by PCR or restriction endonuclease digestion) independent of other sequences. It also includes a recombinant DNA that is part of a hybrid gene encoding additional polypeptide sequence.

By "transformation," "transfection," or "transduction" is meant any method for introducing foreign molecules into a cell. Lipofection, DEAE-dextran-mediated transfection, microinjection, protoplast fusion, calcium phosphate precipitation, transduction (*e.g.*, bacteriophage, adenoviral retroviral, or other viral delivery), electroporation, and biolistic transformation are just a few of the methods known to those skilled in the art that can be used in the invention.

By "transformed cell," "transfected cell," or "transduced cell," is meant a cell (or a descendent of a cell) into which a nucleic acid molecule (*e.g.*, a DNA or RNA molecule) encoding a polypeptide of the invention has been introduced by means of recombinant DNA techniques.

By "promoter" is meant a minimal sequence sufficient to direct transcription. Promoter elements that are sufficient to render promoter-dependent gene expression controllable for cell type-specific, tissue-specific, temporal-specific, or inducible by external signals or agents can also be used in the invention; such elements can be located in the 5' or 3' or intron sequence regions of the native gene.

By "operably linked" is meant that a gene and one or more regulatory sequences are connected in such a way as to permit gene expression when the appropriate molecules (*e.g.*, transcriptional activator proteins) are bound to the regulatory sequences.

By "expression vector" is meant a genetically engineered plasmid or virus, derived from, for example, a bacteriophage, adenovirus, retrovirus, poxvirus, herpesvirus, or artificial chromosome, that is used to transfer a peptide or polypeptide coding sequence (*e.g.*, a CYP1B1 peptide coding sequence), operably linked to a promoter, into a host cell, such that the encoded peptide or polypeptide is expressed within the host cell.

Other features and advantages of the invention will be apparent from the drawings, following detailed description, and the claims.

Brief Description of the Drawings

Fig. 1 is a graph showing the level of peptide binding of MAGE-3, CYP239, and CYP246 to TAP-deficient T2 cells.

Figs. 2A-2D are graphs showing that CTL derived from healthy donors recognize CYP239 and CYP246 peptides. (A) CTL raised against the CYP239 peptide specifically lyse CYP239 pulsed (■), but not unpulsed T2 cells (□), or T2 cells pulsed with an irrelevant peptide (O; F271 from MAGE-3). (B) Similarly, CTL generated against the CYP246 peptide recognize only T2 cells pulsed with CYP246 (■), but not control T2 cells (□, unpulsed; O, pulsed with F271). The diagrams display representative experiments for 11/13 healthy donors positive for CYP239-specific CTL induction and 4/10 healthy donors positive for CYP246-specific CTL induction. (C) CYP239-specific CTL recognize autologous CD40-B cells pulsed with CYP239 peptide (◆), but not unpulsed autologous CD40-B (◇) or allogeneic HLA-A2 mismatched CD40-B unpulsed (O) or pulsed with CYP239 peptide (●). (D) Analogous results were obtained for CYP246-specific CTL using the same target cells unpulsed or pulsed with the CYP246 peptide.

Fig. 2E is a series of graphs showing a representative tetramer analysis of CYP239- and CYP246-specific CTL after 4 weeks in culture. The A2/TAX tetramer served as a negative control. Percent tetramer$^+$ CD8$^+$ T cells is shown. Positive tetramer staining correlated with specific cytotoxicity in ^{51}Cr assays.

Fig. 2F is a graph showing the cytotoxicity of expanded CYP239-specific tetramer sorted CTL against T2 cells either unpulsed (□), pulsed with CYP239 (■) or RT-pol476 (O).

Fig. 3 is a graph showing the level of specific lysis of CD40-activated B cells that were titrated with increasing concentrations of peptide before exposure to peptide-specific CTLs.

Figs. 4A-4H are graphs showing that CYP239 and CYP246-specific CTL are cytotoxic for HLA-A2$^+$ melanoma, multiple myeloma and ovarian carcinoma cell lines. Expression of CYP1B1 in all tumor cell lines was confirmed by Western blot analysis. HLA-A2$^+$ cell lines are shown by solid symbols; HLA-A2$^-$ cell lines by open symbols. Targets for CYP239-specific CTL (upper panel) and CYP246-specific CTL (lower panel) were (A, B) melanoma cell lines K029 (●) and SK-MEL-2 (○), (C, D) multiple myeloma cell lines U266 (●), IM-9 (◆) and HS-Sultan (◇), and (E, F) ovarian carcinoma cell lines 36M (■) and SK-OV-3 (□). Normal cells including the HLA-A2$^+$ fibroblast cell line GM847 (△) and primary monocytes from 3 HLA-A2$^+$ (○, ◇, ▽) and one HLA-A2$^-$ healthy donors (□) were not lysed by either (G) CYP239-specific or (H) CYP246-specific CTL. Results of one representative experiment are shown. Similar results were obtained for each of 2 to 6 CTL tested per target.

Fig. 5 is a graph showing the specific lysis of tumor cells pulsed with CYP239 by CYP239-specific CTLs.

Figs. 6A-6C are graphs showing lysis of CYP1B1$^+$ HLA-A2$^+$ primary lymphoma and acute myeloid leukemia (AML). Two HLA-A2$^+$ CYP1B1$^+$ follicular lymphoma samples (■ and ●) from lymph node biopsies were lysed by (A) CYP239-specific and (B) CYP246-specific CTL, while no cytotoxicity occurred against an HLA-A2$^-$ CYP1B1$^+$ FL (□). Experiments were performed from two different normal donors with similar results. (C) CYP239-specific CTL lysed primary HLA-A2$^+$ (◆), but not HLA-A2$^-$ (◇) AML cells.

Figs. 7A and 7B are each a series of graphs showing the generation of CYP239- and CYP246-specific CTL from cancer patients. (A) CYP239-specific CTL from 4 patients (pt 1-4) and CYP246-specific CTL from pt 3 and pt 4 lysed T2 cells pulsed with the immunizing peptide (■), but not unpulsed T2 cells (□) or T2 cells pulsed with the irrelevant F271 peptide from MAGE-3 (○). (B) The same CYP239- or CYP246-specific CTL lysed the CYP1B1$^+$ HLA-A2$^+$ myeloma cell lines IM-9 (◆) and U266 (●) but not the CYP1B1$^-$ HLA-A2$^-$ line HS-Sultan (◇). In two cases, IM-9 cells were not lysed. All experiments shown here were performed twice with similar results.

Fig. 8 is a graph showing that the efficacy of a combination of CYP1B1 and hTERT-specific CTL in a chromium release assay. CYP239- and I540-specific CTL were used individually or in combination against a mixture of T2 cells pulsed with either CYP239 or I540 peptide. Target cells were mixed at a 1:1 ratio using a final number of 5000 cells/well. Numbers shown reflect the number of effector cells added to each well.

Fig. 9 is a graph showing the specific lysis of target cells with CTLs specific for heteroclitic peptides CYP239-19 and CYP239-139.

Fig. 10 is a graph showing the stability of HLA-A2/peptide complexes including the indicated peptides, as determined by TAP-deficient T2 cell assays.

Fig. 11 is a graph showing the stability of HLA-A2/peptide complexes including CYP190 and CYP528, as determined by TAP-deficient T2 cell assays.

Figs. 12A-12C are graphs showing that CYP190-specific CTL lyse peptide-pulsed T2 cells (A), HLA-$A2^+$ myeloma cell lines, and HLA-$A2^+$ primary ALL cells (C).

Figs. 13A and 13B are graphs showing that CYP190-specific CTL can be generated from cancer patients, such as a (A) prostate cancer patient (HLA-$A2^+$), and (B) a multiple myeloma patient (HLA-$A2^+$).

Fig. 14 is a graph showing the generation and verification of CYP1B1-specific tetramers including CYP239, CYP246, or a control, Tax 11.

Fig. 15 is a schematic representation of a system to detect CYP1B1 T cells by HLA-A2/peptide tetrameric complexes.

Fig. 16 is a set of graphs showing the detection of CYP1B1-specific CTL in normal HLA-$A2^+$ donors.

Fig. 17 is a set of graphs showing the detection of CYP1B1-specific CTL in HLA-$A2^+$ multiple myeloma patients.

Detailed Description

We have discovered that cytochrome P450 1B1 (CYP1B1) includes peptides that bind to HLA molecules. Antigen presenting cells (APCs) that present such peptides on their surfaces, in complexes with HLA, can activate

cytotoxic T lymphocytes (CTLs) to specifically lyse cells expressing CYP1B1, in an MHC-restricted fashion. The invention thus provides methods for immunotherapeutic targeting of CYP1B1-expressing cells, such as cancer cells, and methods of monitoring the efficacy of such therapeutic methods.

Based on our observations that CYP1B1 is a mediator of dioxin-related effects on tumorigenesis, in combination with searches of public literature databases, such as PubMed, we identified CYP1B1 as a potential universal tumor antigen. It is overexpressed in nearly 100% of human tumors (Murray *et al.*, Cancer Res. 57:3026-3031, 1997), whereas the expression in normal tissue is low and limited to steroidogenic and steroid-responsive tissue (Buters *et al.*, Proc. Natl. Acad. Sci. USA 96:1977-1982, 1999). CYP1B1 is a member of the superfamily of monooxygenases responsible for the metabolic activation of environmental carcinogens. Mice lacking CYP1B1 have a much lower incidence of lymphoma than wild type mice after challenge with polycyclic aromatic hydrocarbons, further implicating that CYP1B1 plays a role in oncogenesis.

T cell mediated anti-tumor immunity

As is noted above, there is considerable evidence that human T cells can specifically lyse tumor cells (Rosenberg, Immunity 10:281-287, 1999). Most attention has been focused on $CD8^+$ CTLs as the principle effector cells of antigen-specific anti-tumor immunity. Chief among the recent discoveries that have helped propel clinical efforts has been the characterization of tumor associated antigens (TAAs) (Boon *et al.*, Annual Review of Immunology 12:337-365, 1994). Pioneering studies in the early 1990s demonstrated the existence of human TAAs using patients' CTLs that recognized peptides derived from these antigens (Van Pel *et al.*, Immunological Reviews 145:229-250, 1995; Rosenberg, Immunol. Today 18:175-182, 1997). Although these studies primarily focused on melanoma, TAAs have been subsequently characterized in several other malignancies (Van Pel *et al.*, Immunological Reviews 145:229-250, 1995; Rosenberg, Immunol. Today 18:175-182, 1997; Van den Eynde *et al.*, Curr. Opin. Immunol. 9:684-693, 1997), raising the hypothesis that most, if not all,

tumors express antigens that CTL can potentially attack. The demonstration that TAA-specific immune responses can lead to tumor regression has been borne out extensively in animal models (Rosenberg, Immunity 10:281-287, 1999). Although the identification of TAAs using patients' CTLs has revitalized the field of T cell immunotherapy, these methods are slow, very expensive, and labor-intensive. Moreover, the strategy relies on the generation of tumor-specific T cell clones *in vitro*, suggesting that only a restricted set of TAAs will be identified by this method. With these limitations in mind, Pfreundschuh and colleagues developed an alternative approach, SEREX (serological identification of antigens by recombinant expression cloning), to identify TAAs (Sahin *et al.*, Curr. Opin. Immunol. 9:709-716, 1997). SEREX makes use of patients' antibody responses to tumor-derived genes and this strategy has accelerated the identification of TAAs significantly. Although several T cell-defined TAAs, such as the MAGE genes, have also been identified by SEREX, there is no information available about CTL epitopes for the vast majority of genes in the SEREX database, and, of course, such epitopes are required to activate a CTL response.

Although there is no doubt that the identification of numerous TAAs by CTL-based approaches or SEREX reflects the existence of an anti-tumor immune response, it remains to be determined if these antigens play a role as tumor regression antigens (Sarma *et al.*, J. Exp. Med. 189:811-820, 1999). As is mentioned above, most T cell epitopes in TAAs identified by patient CTLs have been demonstrated to be of low MHC binding affinity and/or low MHC/peptide complex stability. Clinical vaccination trials have circumvented this obstacle by utilizing altered peptides with higher MHC binding affinity and higher MHC/peptide complex stability (Rosenberg *et al.*, Nat. Med. 4:321-327, 1998). This quality distinguishes TAA-derived peptides from viral peptides that are almost exclusively of high binding affinity and high MHC/peptide complex stability (Feltkamp *et al.*, Mol. Immunol. 31:1391-1401, 1994; Sette *et al.*, J. Immunol. 153:5586-5592, 1994). The low binding affinity of TAA-derived peptides is likely to be one of the reasons why natural CTL responses against such peptides are not successful for tumor eradication. This is in agreement with the

finding that large numbers of TAA-specific CTLs co-exist with metastatic tumors in melanoma patients (Romero *et al.*, J. Exp. Med. 188:1641-1650, 1998). A recent study has even demonstrated that despite expansion, such CTLs were hyporesponsive, showing reduced cytotoxic and cytokine responses (Lee *et al.*, Nat. Med. 5:677-685, 1999).

To overcome these limitations of currently known TAAs, we have developed methods to identify more universal TAAs, and, in particular, those containing T cell epitopes with high MHC binding affinity and high MHC/peptide complex stability. Such TAAs and MHC-binding peptides thereof can trigger sufficient CTL responses against a broad range of tumor types. Rather than analyzing tumor-derived T cell clones or tumor-specific antibodies derived from patients, an alternative strategy was used, in which TAA and their CTL epitopes are deduced from genes known to be selectively expressed in tumors. By combining bioinformatics to predict peptides that bind to HLA with high affinity, peptide binding analysis, and a powerful *in vitro* T cell expansion system, the cytochrome P450 1B1 (CYP1B1) was identified (see below). This TAA contains at least two peptide epitopes that (1) bind to HLA-A*0201 with high affinity and high MHC/peptide complex stability, (2) are naturally processed and presented by HLA-A*0201 molecules on the cell surface of a panel of tumor cell lines, (3) elicit peptide-specific HLA-restricted CTL responses, and (4) are recognized by such CTL on a wide variety of different tumor histologies.

Deducing CTL epitopes in tumor associated antigens (TAAs): Making use of genomics and proteomics for tumor immunology

Current developments in genomics and proteomics suggest that numerous TAA candidate genes can be identified. The Human Genome Project (HGP), the Human Cancer Gene Anatomy Project (CGAP), the SEREX database, and other databases, including literature databases such as PubMed, provide an enormous set of data that can be analyzed to identify genes that fulfill the criteria of universal tumor antigens, as are described above. It is clear that entering the post-genomic era, none of the classical approaches to characterize TAA, including

T cell cloning and testing of T cell clones against expression libraries (Boon *et al.*, Annual Review of Immunology 12:337-365, 1994), is suitable for the analysis of the ever-growing databases to identify a set of universal tumor antigens.

To overcome the limitations of prior methods in determining CTL epitopes, advances in bioinformatics can be applied. First, database mining and integration can be used to identify of universal tumor antigen candidates, which are genes that are expressed at a much higher level in tumor cells than in normal cells. Then, computational methods are used to predict peptides derived from these proteins for high-affinity binding to MHC molecules. The requirements for peptides to bind to class I HLA molecules and to elicit CTL responses have been studied extensively (Rammensee *et al.*, Annual Review of Immunology 11:213-244, 1993; Sidney *et al.*, Immunology Today 17:261-266, 1996). The strength of $CD8^+$ CTL responses depends upon the binding affinity of the target peptide to MHC, the peptide-MHC complex stability, and the avidity of T cell receptor (TCR) binding for the peptide complex (Sette *et al.*, J. Immunol. 153:5586-5592, 1994; van der Burg *et al.*, J. Immunol. 156:3308-3314, 1996; Savage *et al.*, Immunity 10:485-492, 1999; Gallimore *et al.*, Eur. J. Immunol. 28:3301-3311, 1998). These factors directly influence the efficiency of peptide loading and the number of peptides expressed on the cell surface (Gallimore *et al.*, Eur. J. Immunol. 28:3301-3311, 1998). The vast majority of viral-derived immunodominant peptides are of high binding affinity and/or peptide-HLA complex stability (Feltkamp *et al.*, Mol. Immunol. 31:1391-1401, 1994; Sette *et al.*, J. Immunol. 153:5586-5592, 1994). Since only a very small portion of peptides can bind to MHC molecules, rapid and accurate methods to identify them, such as those used in the present invention, can expedite the search for CTL epitopes by orders of magnitude.

A great deal of effort has been expended on the development of computational methods to identify peptides that bind strongly to various MHC alleles. It began with the work of Rammensee and colleagues, who identified motifs in peptide sequences that serve as signatures of the MHC molecules to which they bind (Rammensee *et al.*, Immunogenetics 41:178-228, 1995). Motif-

based methods have recently been applied to the identification of CTL epitopes deduced from proteinase 3 (Molldrem *et al.*, Blood 88:2450-2457, 1996), MAGE-3 (Nijman *et al.*, Eur. J. Immunol. 23:1215-1219, 1993), MUC-1 (Brossart *et al.*, Blood 93:4309-4317, 1999), and telomerase (PCT/US99/25438). Typically, only 20% of peptides that carry the motif bind to the respective MHC molecule. The inclusion of "secondary anchor" positions (Ruppert *et al.*, Cell 74:929-937, 1993), the so-called extended motif, significantly improves the specificity of motif-based methods, but they are available only for HLA-A*0201 (Ruppert *et al.*, Cell 74:929-937, 1993) and HLA-B*3501 (Schönbach *et al.*, J. Immunol. 154:5951-5958, 1995). Many other statistically-based computational methods have been developed (for reviews, see, *e.g.*, Hammer, Curr. Opin. Immunol. 7:263-269, 1995; Parker *et al.*, Immunol. Res. 14:34-57, 1995), including the polynomial method (Gulukota *et al.*, J. Mol. Biol. 267:1258-1267, 1997), methods based on neural nets (Gulukota *et al.*, J. Mol. Biol. 267:1258-1267, 1997; Brusic *et al.*, Bioinformatics 14:121-130, 1998; Brusic *et al.*, Nucleic Acids Res. 26:368-371, 1998), a method that assigns a score for each amino acid at each position as determined experimentally *via* single residue substitutions (Hammer *et al.*, J. Exp. Med. 180:2353-2358, 1994), and a method developed by Parker *et al.* based on a database of the half-lives of bound β2-microglobulin (β2m) in MHC-peptide complexes (Parker *et al.*, J. Immunol. 152:163-175, 1994). The method developed by Parker *et al.* assumes that the dissociation of β2m is rate-limited by the dissociation of peptide, so that variation in the microglobulin half-life reflects variation in the peptide half-life. The variation is, in turn, assumed to reflect the variation in the binding affinity of the peptide. A weight matrix is then determined to best reflect the half-lives, assuming that the contribution of one peptide position does not depend on its neighboring positions.

Weng and colleagues have recently developed a new statistical method (implemented as a computer program named LPpep; Weng *et al.*, http://bioinformatics.bu.edu/peptides.html) to predict strong HLA-A*0201-binding peptides. It determines the contributions for each of the 20

amino acids at each of the positions of a peptide using a linear programming algorithm. When tested on a data set of over 1000 peptides having known binding affinities, LPpep has a higher sensitivity (>0.75) and specificity (> 0.9) than four other available methods.

High volume analysis of peptide MHC affinity and MHC/peptide complex stability

The basic principles of peptide binding to MHC molecules have been well established in the field (Rammensee *et al.*, Annual Review of Immunology 11:213-244, 1993; Rothbard *et al.*, Annual Review of Immunology 9:527-565, 1991; Engelhard, Annual Review of Immunology 12:181-207, 1994; Madden, Annual Review of Immunology 13:587-622, 1995; Pamer *et al.*, Annual Review of Immunology 16:323-358, 1998; Rock *et al.*, Annual Review of Immunology 17:739-779, 1999), and numerous assay systems have been developed to analyze the binding of any given peptide to MHC molecules. Binding has been analyzed using intact TAP-deficient cells (Salter *et al.*, EMBO J. 5:943-949, 1986; Schumacher *et al.*, Cell 62:563-567, 1990) and by *in vitro* assays utilizing purified HLA molecules (Ruppert *et al.*, Cell 74:929-937, 1993; Schumacher *et al.*, Cell 62:563-567, 1990; Townsend *et al.*, Cell 62:285-295, 1990). While most assay systems have focused on the maximal binding affinity, it has recently been suggested that the dissociation rate of MHC and peptide (also measured as MHC/peptide complex stability) may be a more important determinant for characterizing a peptide as a dominant T cell epitope (van der Burg *et al.*, J. Immunol. 156:3308-3314, 1996; Busch *et al.*, J. Immunol. 160:4441-4448, 1998; Kammer *et al.*, J. Exp. Med. 190:169-176, 1999).

In vitro analysis of CTL responses

The generation of antigen-specific T cells *in vitro* is a classical immunological technique. Antigen-specific T cells can be generated relatively easily if the peptides used to make such cells are: (1) immunodominant, (2) of viral or other non-self origin, (3) expressed at a reasonably high copy number on the cell surface (Porgador *et al.*, Immunity 6:715-726, 1997), and (4) of high

affinity for, and of low dissociation rate (high MHC/peptide complex stability) from, MHC, and if the T cell pool under study has been exposed to the antigen *in vivo* prior to *ex vivo* analysis (recall response). The frequency analysis of peptide-specific T cells by tetramer technology (see below) revealed a significantly higher frequency than earlier assays based on *in vitro* expansion had suggested.

It is therefore apparent that only a fraction of specific CTLs are expanded in classical *in vitro* systems utilizing unstimulated peripheral blood mononuclear cells (PBMC) as antigen presenting cells (McMichael *et al.*, J. Exp. Med. 187:1367-1371, 1998). To circumvent these pitfalls, *in vivo* systems utilizing transgenic mice carrying human HLA genes have been introduced (Man *et al.*, International Immunology 7:597-605, 1995; Wentworth *et al.*, International Immunology 8:651-659, 1996; Alexander *et al.*, J. Immunol. 159:4753-4761, 1997). However, these systems are expensive and are not suitable for screening multiple peptide epitopes simultaneously. Making use of new findings in basic immunology, it is possible to optimize further currently available *in vitro* culture technology. The use of an APC instead of PBMC as stimulators is only one example.

We have developed a system that utilizes dendritic cells (DC) for primary activation and CD40-activated B cells (CD40-B) for re-stimulation, thereby mimicking the physiological sequence of events between T cells and APCs during an ongoing immune response (Schultze *et al.*, J. Exp. Med. 89:1-12, 1999; Schultze *et al.*, J. Clin. Invest. 100:2757-2765, 1997). This system has been successfully used for the identification of T cell epitopes derived from hTERT and the clonal immunoglobulin in B cell malignancies (PCT/US99/25438). From a single blood draw, professional APCs, including DCs and CD40-activated B cells, are generated, and the remaining PBMCs are enriched for $CD8^+$ T cells. T cells are primarily stimulated with peptide-pulsed DC, and repeatedly stimulated with peptide-pulsed CD40-B cells. Peptide-specificity and HLA-restriction is analyzed after a total of 2-5 stimulations, depending on the antigen under study. This system is not only very powerful in amplifying rare T cells against

TAA-derived peptides, but has several other advantages: (1) it is relatively cheap compared to transgenic mice, (2) a single blood draw is sufficient to generate all cellular components necessary, and (3) the use of professional APCs for restimulation is superior to PBMC.

Classically, the function of CTLs *in vitro* has been defined by cytotoxicity assays using radioactive chromium. Clearly, cytotoxicity analysis is an important component of the characterization of a novel TAA, since tumor cell lysis is the ultimate goal of any TAA-directed immunotherapeutic intervention. However, such assays are not suitable to determine the frequency of peptide-specific CTLs. In addition, the sensitivity of cytotoxicity assays to identify very small numbers of specific CTLs is insufficient. To detect very low numbers of specific CTLs and to determine their frequency, two new technologies, namely the tetramer technology (Altman *et al.*, Science 274:94-96, 1996) and cytokine ELISPOT analysis (Herr *et al.*, J. Immunol. Methods 203:141-152, 1997), have been developed and applied to tumor immunology. In particular, tetramers have been suggested as a tool to enrich CTL lines for peptide-specific CTL (Dunbar *et al.*, Curr. Biol. 8:413-416, 1998; Yee *et al.*, J. Immunol. 162:2227-2234, 1999; Valmori *et al.*, Cancer Res. 59:2167-2173, 1999). Currently, the tetramer technology is still technically demanding and it is not possible to generate numerous tetramers in small quantities to screen peptide-specific CTL responses against a larger set of unknown peptides. For this purpose, cytokine ELISPOT is more suitable (Herr *et al.*, J. Immunol. Methods 203:141-152, 1997).

Experimental Results

The dioxin-inducible cytochrome P450 1B1 (CYP1B1)

Using the methods described above (also see PCT/US99/25438), we identified the dioxin-inducible cytochrome P450 1B1 (CYP1B1) as a potential TAA. A list of peptides predicted to bind to all HLA alleles available are listed in the Sequence Appendix. The prediction was carried out using three different algorithms that are freely available on the Internet:

http://engpub1.bu.edu/LPpep-cgi/peptide2.cgi

http://www.uni-tuebingen.de/uni/kxi/

http://bimas.dcrt.nih.gov/molbio/hla_bind/

Analysis of the CYP1B1 sequence by two independent prediction algorithms (BIMAS and LPpep, see Experimental Methods, below) revealed two peptides (CYP239 and CYP246) predicted to bind to HLA-A*0201, the most common HLA allele (Table 1). These peptide sequences are unique in the public gene databases and in particular are not found within any other member of the cytochrome P450 family. (Also see below for additional CYP1B1 peptides (*e.g.*, CYP190 and CYP528) identified according to the invention.)

Peptide binding of CYP1B1 derived peptides

Binding of both peptides to HLA-A2, as well as their complex stability, was determined using a cellular assay employing TAP-deficient T2 cells (Table 1; PCT/US99/25438). Both peptides stabilized HLA-A2 molecules on the surface of T2 cells to a similar extent as a positive control peptide (F271) derived from the tumor antigen MAGE-3 (Nijman *et al.*, Eur. J. Immunol. 23:1215-1219,1993), which is known to bind HLA-A2 with high affinity. In particular, T2 cells were incubated with peptide in serum-free medium for up to 18 hours, harvested, washed, and subsequently stained with FITC-labeled anti-HLA-A2 mAb BB7.2 (maximum peptide binding). Increase in fluorescence intensity was determined as a function of peptide binding. For analysis of complex stability, T2 cells were cultured in serum-free media for an additional 2, 4, 6, or 24 hours, and subsequently analyzed for HLA-A2 expression by flow cytometry. As is shown in Fig. 1, the MAGE-3-derived peptide, which induces CTL responses in the majority of all normal donors, demonstrated high binding affinity and complex stability. Although both CYP1B1-derived peptides bound to HLA-A2, CYP246 showed a significantly lower complex stability than CYP239 and MAGE-3. Moreover, attempts to induce CTL responses were successful in 13/15 donors against CYP239, but only 4/9 donors for CYP246. Our data further show that

complex stability might be a more important factor than binding affinity for the likelihood to generate peptide-specific CTL responses.

TABLE 1

Binding of CYP1B1 and control peptides to human HLA-A*0201

sequence	BIMAS[1]	LPpep[2]	binding affinity[3] [FI]
SLVDVMPWL	1108	2.88	3.8
WLQYFPNPV	1216	6.23	3.4
FLWGPRALV	2655	7.63	3.2

1 Peptide prediction at BIMAS (BioInformatics & Molecular Analysis Section): scores for predicted binding are calculated as half-life of MHC/peptide complexes (peptides with scores > 500 were chosen as potential candidates).

2 LPpep (peptide prediction at Boston University): scores are predicted as arbitrary $\ln(IC_{50})$ concentrations (peptides with scores < 7 were chosen as potential candidates).

3 Mean fluorescence with peptide / mean fluorescence without peptide - 1. Results representative of 4 experiments.

Peptide-specific killing

To test whether CYP239 and CYP246 reactive T cells are present in the human T cell repertoire, CTL lines were generated *ex vivo* by repetitive stimulation with peptide pulsed autologous APC. CTL specific for CYP239 were induced from peripheral blood mononuclear cells (PBMC) in 11 of 13 healthy HLA-A2$^+$ donors (Fig. 2A). These CTL specifically lysed T2 cells pulsed with CYP239 peptide, while no cytotoxicity occurred against unpulsed T2 cells or T2 cells pulsed with the F271 peptide from MAGE-3. CYP246 specific CTL were generated in 4 of 10 healthy HLA-A*0201$^+$ donors (Fig. 2B). HLA-A2 restriction was demonstrated using autologous and HLA-A2 mismatched CD40-activated B cells (CD40-B) as targets (Figs. 2C and 2D). CYP239-specific CTL lysed autologous CD40-B pulsed with CYP239, but not allogeneic HLA-A2- CD40-B pulsed with CYP239 (Fig. 2C). Similar results were obtained for CYP246-specific CTL (Fig. 2D).

Experiments titrating the concentration of peptide onto the CD40-activated B cells before the cytotoxicity assay further support the peptide-specificity of the CTL generated against the CYP239 peptide. Comparing the data with published data in the literature the cell line tested in this experiment is of intermediate avidity. Alternatively, the cell line contains both high and low avidity CTL and the curve represents the sum of the actions of these CTLs (Fig. 3).

For both CYP239 and CYP246 CTL, specificity was further demonstrated using peptide/MHC tetramers (Fig. 2E). Frequency analysis using CYP239 tetramers demonstrated that 1.4-2.4% of all $CD8^+$ T cells recognized the CYP239 peptide, a percentage comparable to previously published data for gp100 specific (Yee *et al.*, J. Immunol. 162:2227-2234, 1999) or proteinase-3 specific CTL lines (Molldrem *et al.*, Cancer Res. 59:2675-2681,1999). CYP246-specific CTLs were detected with CYP246 tetramer, but the frequency of specific CTL was lower (0.47%). To further confirm peptide-specific cytotoxicity, CYP239 tetramer-positive CTL were sorted and expanded using phytohemagglutinin (PHA), IL-7, IL-2, and irradiated allogeneic PBMC. These CTL lysed T2 cells pulsed with CYP239 at extremely low E:T ratios, but not unpulsed T2 cells or T2 cells pulsed with an irrelevant HLA-A2 binding peptide (Fig. 2F). Thus, CYP1B1 contains at least two HLA-A*0201 binding peptides, and T cells recognizing these peptides are present in the T cell repertoire of healthy donors.

CYP1B1 specific CTL lyse CYP1B1 expressing tumors in an HLA-A2 restricted fashion

Although peptide-specificity of CTL is demonstrated by lysis of peptide-pulsed target cells, it is important to show that tumor cells themselves process and present the peptide in the groove of their MHC molecules (Yee *et al.*, J. Immunol. 162:2227-2234, 1999). We approached this question by using a panel of HLA-$A2^+$ and HLA-$A2^-$ tumor cell lines that all express CYP1B1 protein. CYP239- and CYP246-specific CTL from healthy donors were then screened for cytotoxicity (Figs. 4A-4H). CYP239 CTL (Fig. 4A) and CYP246 CTL (Fig. 4B) showed

specific lysis of HLA-A2$^+$ melanoma cell line K029, but not HLA-A2$^-$ SK-MEL-2 cells. Similarly, the HLA-A2$^+$ myeloma cell lines IM-9 and U266 were lysed by CYP239 CTL (Fig. 4C) and CYP246 CTL (Fig. 4D), while the HLA-A2$^-$ myeloma HS-Sultan cell line was not killed. Finally, specific cytotoxicity by CYP239 CTL (Fig. 4E) and CYP246 CTL (Fig. 4F) was observed against the HLA-A2$^+$ ovarian carcinoma cell line 36M, but not the HLA-A2$^-$ line SK-OV-3. These data show that CYP1B1 derived peptides are naturally processed and presented by tumor cell lines of different tissue origin.

Since CYP1B1 expression has been reported in fibroblasts (Eltom *et al.*, Carcinogenesis 19:1437-1444, 1998) and monocytes (Baron *et al.*, Biochem. Pharmacol. 56:1105-1110, 1998), we analyzed an HLA-A2$^+$ fibroblast cell line (GM847) and primary peripheral blood derived monocytes from four healthy donors as targets for CYP1B1-specific CTL. Western blot analysis showed that of these normal cells express low or absent levels of CYP1B1. As is shown in Figs. 4G and 4H, CYP239 and CYP246-specific CTL failed to lyse these normal targets. In contrast, CD40-activated B cells strongly express CYP1B1 protein (detected by Western blot), but these normal cells were not lysed by CYP239- or CYP246-specific CTL (Figs. 2C and 2D), suggesting that there is a differential expression of CYP1B peptides on tumor cells.

Methods to improve killing of tumor cell lines

The experiments described so far suggest that CYP239 peptide is most likely expressed at low levels on tumor cell MHC. Alternatively, tumor cells could be more resistant to CTL-mediated lysis. To address these issues and to determine whether the increase of peptide on the cell surface of tumor cells would lead to increase killing of the tumor cells, tumor cells were pulsed with the specific peptide before they were used in chromium release assays. We could demonstrate that peptide-pulsing of tumor cells significantly increased killing of the target cells, suggesting that the level of naturally expressed CYP239 peptide is low on the tumor cells, however, that these cells can be readily killed once the level of peptide is increased. This also suggests that any methodology to increase

the expression of CYP1B1-derived peptides on the cell surface will make the tumor cell a susceptible target for CYP1B1-specific CTLs (Fig. 5).

Lysis of primary HLA-A2$^+$ follicular lymphoma cells

CYP1B1-specific CTLs were then evaluated for cytotoxicity against primary tumor tissue. Because CYP1B1$^{-/-}$ mice demonstrate a significantly reduced incidence in carcinogen-induced lymphomas (Buters *et al.*, Proc. Natl. Acad. Sci. U.S.A. 96:1977-1982, 1999), we chose to study human primary follicular lymphoma (FL) as a model tumor target for CYP1B1 specific CTL. Tumor cells from two HLA-A2$^+$ FL samples and one HLA-A2$^-$ FL sample were found to be CYP1B1$^+$ as assessed by Western blot analysis. Using these target cells, we found that CTL lines generated against CYP239 or CYP246 were cytotoxic for the HLA-A2$^+$ FL, while no killing of the HLA-A2$^-$ FL was observed (Figs. 6A and 6B). We also demonstrated lysis of HLA-A2$^+$ primary acute myeloid leukemia (AML) cells, but not HLA-A2$^-$ primary AML cells by CYP239 CTL (Fig. 6C). These data show that both CYP1B1-derived peptides are processed and presented by HLA-A2 on primary tumor cells and that HLA-A2 restricted CYP1B1 specific CTL from healthy donors can recognize and kill these target cells.

Generation of CYP1B1-specific CTL from patients with multiple myeloma

Similar to experiments described for healthy donors, we next attempted to generate CYP1B1-specific CTL from peripheral blood of cancer patients. HLA-A2$^+$ patients with multiple myeloma (n=3) or follicular lymphoma (n=1) (Table 2) were tested for *ex vivo* generation of CYP239 (n=4) or CYP246 (n=2) specific CTL. Generation of all cellular components of our *ex vivo* system (*i.e.*, dendritic cells, CD40-B, and CTL), as well as expansion of CTL to CYP239 and CYP246 were similar to results obtained for healthy donors. Using peptide-pulsed T2 cells as targets, we demonstrated CYP239-specific CTL in all four patients (Fig. 7A). Due to lower numbers of PBMC available, CYP246-specific CTL cultures were only initiated in patients 3 and 4. CYP246-specific CTLs were

detected in both patients. These patient-derived lines showed tumor-specific lysis of HLA-A2$^+$ myeloma cell lines U266 and IM-9, but not the HLA-A2$^-$ myeloma cell line HS-Sultan (Fig. 7B). Because autologous tumor cells were not available from these patients, we tested the same FL samples described above as primary tumor targets. CYP239-specific CTL from patient 1 lysed both HLA-A2$^+$ FL samples but not the HLA-A2$^-$ (18% *vs.* 0% at an E:T ration of 30:1).

TABLE 2

patient	age	sex	disease	stage	prior treatment	CTL induction CYP239	CTL induction CYP246
1	41	f	Multiple Myeloma	I A	none	yes	ND
2	47	f	Multiple Myeloma	II A	none	yes	ND
3	40	m	Multiple Myeloma	III A	High-Dose Dexamethasone, discontinued >30d prior to leukapheresis	yes	yes
4	29	m	Non Hodgkin's Lymphoma (Follicular Lymphoma)	III A	none	yes	yes

Patient characteristics, prior treatment, and CTL induction

ND = not determined

Combining CYP1B1- and hTERT-specific CTL

We next analyzed the combination of CYP1B1-specific CTL with hTERT-specific CTL (Vonderheide *et al.*, Immunity 10:673-679, 1999). To normalize for equal susceptibility to T-cell mediated lysis, we used a mixture (1:1 ratio) of T2 cells pulsed with either CYP239 or I540 hTERT peptide (Vonderheide *et al.*, Immunity 10:673-679, 1999) as a model for heterogeneous antigen expression. Equal ^{51}Cr labeling of both T2 cell populations was assured. Under these conditions, it is expected that either CTL line alone can only lyse a maximum of 50% of the target cell population while the combination if effective has the potential to kill >50% of all cells (Janeway, *Immunobiology: The Immune System in Health and Disease* (Garland Publishing c/o Taylor & Francis, Inc.,

New York, 1999), p. 297). This is true for specific lysis regardless of the E:T ratio used. As postulated, the combination of CYP239- and I540-specific CTL was superior to each CTL line alone, achieving specific lysis of >50% (Fig. 8). Similar observations were made in independent experiments using CTL generated from two different donors. We also analyzed the effect of combined CYP1B1 and hTERT CTL on the HLA-$A2^+$ tumor cell line IM-9, which expresses both antigens. In two experiments, we observed additive lysis of CYP239- and I540-specific CTL across a range of E:T ratios. These data demonstrate the potential of enhancing antigen-specific T cell immunity by targeting multiple antigens, such as CYP1B1 and hTERT.

Use of heteroclitic peptides

To improve immunogenicity of CYP1B1 derived peptides, we designed heteroclitic peptides optimized for binding affinity to MHC. We have already shown that CTL generated against the CYP239 wild type peptide can recognize and lyse target cells pulsed with the heteroclitic peptide CYP239-19 equally well, while CTL generated with CYP239 do not recognize CYP239-139. These data show that despite similar binding, the change of a third amino acid does not allow for recognition by CTL specific for CYP239. Most likely, the amino acid change induced a change in the three dimensional structure of the peptide not allowing TCR activation (Fig. 9). To design heteroclitic peptides with higher binding affinity, we used an algorithm available on the Internet (http://engpub1.bu.edu/LPpep-cgi/peptide3.cgi). Two heteroclitic peptides to the immunogenic peptide CYP239 have been designed as examples to improve binding affinity, complex stability, and, potentially, immunogenicity (Table 3).

TABLE 3

Examples of Heteroclitic Peptides Optimized for Binding to HLA-A*0201

heteroclitic 9mers

position	peptide	nmer	Parker score	Zhiping score	T2 assay result
292	YLYAFILSV	9	8948.1	-0.99	n.d.
344	YLYTRYPDV	9	1535.7	0.7	n.d.
380	YLYAFLYEV	9	8948.1	-3.51	n.d.
246	YLYYFPNPV	9	3890.5	-0.27	n.d.
239 (1, 3, 9)	YLYDVMPWV	9	53099.7	-3.42	2.00
239 (1, 9)	YLVDVMPWV	9	16593.6	-0.85	2.16
239 (1, 3)	YLYDVMPWL	9	16309.2	-1.76	n.d.
239 (3, 9)	SLYDVMPWV	9	11543.4	-1.35	n.d.
239 (1)	YLVDVMPWL	9	5096.6	0.81	n.d.
239 (9)	SLVDVMPWV	9	3607.3	1.22	n.d.
239 (3)	SLYDVMPWL	9	3545.5	0.31	n.d.

Peptide binding of heteroclitic CYP239 peptides

The T2 assay described above was used to determine binding and dissociation rate of heteroclitic peptides engineered for optimal binding to HLA molecules. Two heteroclitic peptides to CYP239 were tested and shown to have higher peptide/MHC-complex stabilities, as is shown in Table 4. While the control peptide MAGE-3 and the CYP239 peptide showed no significant binding at 24 hours (0.14 resp. 0.12), both heteroclitic peptides still bound to HLA-A*0201 (0.72 resp. 0.73).

TABLE 4

Examples of heteroclitic peptides optimized for binding to HLA-A*0201

time post-pulsing [hours]		0	2	4	6	
MAGE-3	FLWGPRALV	1.88	1.41	0.93	0.77	0.14
CYP239	SLVDVMPWL	1.91	1.37	0.78	0.58	0.12
CYP239-19	YLVDVMPWV	2.16	1.57	1.31	1.13	0.72
CYP239-139	YLYDVMPWV	2.00	1.51	1.24	1.16	0.73

The following Tables 5 and 6 show predicted mutations to improve HLA-A2 binding of CYP1B1 239 and CYP1B1 246.

TABLE 5

Predict Mutations to Improve HLA-A2 Binding CYP239

Under each position, a list of possible amino acid mutations is given, followed by the change in the predicted ln(IC50) produced by the mutation with respect to the original peptide's score.

		POSITION						
1	2	3	4	5	6	7	8	9
K (0.17)	*	A (1.31)						A (0.60)
M (2.03)		C (1.35)						I (1.36)
F (0.60)		G (0.57)						V (1.66)
Y (2.07)		H (0.78)						
		L (1.63)						
		M (2.00)						
		F (1.40)						
		P (0.19)						
		S (0.55)						
		W (1.38)						
		Y (2.57)						

* indicates best amino acid is already present

Original peptide: SLVDVMPWL, predicted ln(IC50) = 2.88
Top scoring peptide under given constraints: YLYDVMPWV, predicted ln(IC50) = -3.42

TABLE 6

Predict Mutations to Improve HLA-A2 Binding CYP246

Under each position, a list of possible amino acid mutations is given, followed by the change in the predicted ln(IC50) produced by the mutation with respect to the original peptide's score.

	POSITION							
1	2	3	4	5	6	7	8	9
A (1.53)	*	A (1.50)						*
R (1.08)		D (0.10)						
N (0.33)		C (1.54)						
C (0.88)		G (0.76)						
G (1.39)		H (0.97)						
L (0.92)		I (0.16)						
K (1.84)		L (1.82)						
M (3.70)		M (2.19)						
F (2.27)		F (1.59)						
S (1.67)		P (0.38)						
T (0.94)		S (0.74)						
Y (3.74)		W (1.57)						
V (1.21)		Y (2.76)						
		V (0.19)						

* indicates best amino acid is already present

Original peptide: WLQYFPNPV, predicted ln(IC50) = 6.23
Top scoring peptide under given constraints: YLYYFPNPV, predicted ln(IC50) = -0.27

Identification of additional HLA-A2 binding epitopes from CYP1B1

Binding studies were carried out to characterize additional CYP1B1-derived peptides that are predicted to bind to HLA-A2. Table 7, below, shows the sequences of additional peptides that are predicted to bind to HLA-A2.

TABLE 7

Predicted binding of epitopes to HLA-A2
Nonamers predicted to bind to HLA-A*0201

		Parker		LPpep		SYFPEITHI	
position	peptide	score	rank	score	rank	score	rank
25	LLLSVLATV	1006	3	3.54	4	32	1
88	RLGSCPIVV	29	18	4.61	6	20	31
190	FLDPRPLTV	128	11	6.52	15	26	5
239	SLVDVMPWL	1108	2	2.88	2	24	9
246	WLQYFPNPV	1216	1	6.23	12	21	22
292	MMDAFILSA	21	19	3.31	3	20	29
344	LLFTRYPDV	656	4	4.69	7	24	7
377	NLPYVLAFL	270	8	7.1	21	25	6
380	YVLAFLYEA	65	14	1.56	1	20	27
479	QLFLFISIL	283	6	5.66	9	26	4
528	LLDSAVQNL	33	16	4.08	5	26	3

Table 1a

Decamers predicted to bind to HLA-A*0201

		Parker		LPpep		SYFPEITHI	
position	peptide	score	rank	score	rank	score	rank
24	LLLLSVLATV	1006	1	4.55	5	24	1
88	RLGSCPIVVL	20	22	3.08	2	26	3
343	LLLFTRYPDV	656	2	5.6	9	343	7
477	KMQLFLFISI	50	13	1.29	1	19	31
479	QLFLFISILA	18	24	3.86	3	15	67
486	ILAHQCDFRA	49	14	3.87	4	18	36

Table 1b

Peptides were pulsed onto TAP-deficient T2 cells, and the maximum binding and the stability over time were assessed by flow cytometry. As is shown in Fig. 10, CYP190 and CYP528 show the longest half-life on the cell surface. Additional experiments were carried out to characterize these peptides, in particular, CYP190. As is shown in Fig. 11, further binding studies using TAP-deficient T2 cells showed that CYP190/A2 complexes can be detected as long as 24 hours after peptide withdrawal. Moreover, as is shown in Figs. 12A-12C, CYP190-specific CTL can be generated from normal HLA-$A2^+$ donors, and these CTL can lyse peptide-pulsed T2 cells (Fig. 12A), HLA-$A2^+$ myeloma cell lines (Fig. 12B), and HLA-$A2^+$ primary ALL cells (Fig. 12C). In addition, as is shown

in Figs. 13A and 13B, CYP190-specific CTL can be generated from HLA-A2$^+$ cancer patients (Fig. 13A, prostate cancer patient, and Fig. 13B, multiple myeloma patient), and show specific lysis.

We also identified HLA-A3 binding epitopes from CYP1B1. Using the BIMAS server, for example, we identified the peptides shown in Table 8, in which the positive control is a peptide derived from influenza A.

TABLE 8

Peptides predicted to bind to HLA-A3 (BIMAS server)

rank	position	sequence	score
10mers			
1	508	GLTIKPKSFK	90
2	445	FLDKDGLINK	60
3	450	GLINKDLTSR	27
9mers			
1	150	SMMRNFFTR	54
2	408	SVLGYHIPK	27
positive control	NP265	ILRGSVAHK	90

As is shown in Table 9, these peptides were tested in a binding assay to T2 cells transfected with HLA-A3 (NP265= positive control from influenza A). These studies showed that CYP408, CYP445, and CYP150, which are not homologous to other cytochrome P450 isoenzymes, repeatedly bound to HLA-A3.

TABLE 9

Binding assay of peptides to T2 cells transfected with HLA-A3

peptide	FI class I	FI
PBS	15.3	
NP265	19.4	0.27
CYP508	16.4	0.07
CYP408	16.9	0.10
CYP445	19.5	0.27
CYP450	16.8	0.10
CYP150	17.2	0.12
Flu-MP58	34.8	1.27

In further studies, we detected CYP1B1 reactive T cells in HLA-A2+ normal donors HLA-A2+ cancer patients (Fig. 14). Specific binding of tetramers with CYP239 and CYP246 peptides was confirmed on T cell lines generated against the respective peptide. No binding could be detected on T cells generated against an irrelevant peptide. A tetramer containing a peptide from HTLV was used as a negative control.

We also devised a system for detecting CYP1B1-specific T cells by HLA-A2/peptide tetrameric complexes, as is illustrated in Fig. 15. $CD8^+$ T cells from normal $HLA\text{-}A2^+$ myeloma patients (n=10) were isolated and analyzed with HLA-A2/peptide tetrameric complexes directly *ex vivo* and after a 10 day *in vitro* restimulation period with peptide, cytokines, and irradiated PBMC. Viral peptides were used as positive (influenza A, EBV) and negative (HTLV Tax) controls.

As is shown in Fig. 16, T cells from HLA-A2+ healthy donors (n=8) were stained with CYP239 and CYP246 tetramers directly *ex vivo* and 10 days after *in vitro* restimulation with CYP239 or CYP246 peptides. The level of detection on day 10 is at 0.05% as determined from background staining of $HLA\text{-}A2^-$ donors. No expansion of CYP239-specific T cells was detected in healthy donors on day 10 (mean $0.022\% \pm 0.018\%$). CYP246-specific T cells were detected in 2 healthy donors with one rising to 0.5% (mean $0.032\% \pm 0.022\%$).

As is shown in Fig. 17, T cells from HLA-A2+ multiple myeloma patients (n=10) were stained with CYP239 and CYP246 tetramers directly *ex vivo* and 10 days after *in vitro* restimulation with CYP239 or CYP246 peptides. The level of detection on day 10 is at 0.05% as determined from background staining of HLA-A2- donors. 4 patients showed T cells reactive against CYP239 >0.05% on day 10 (mean 0.068%±0.055%), whereas 5 patients showed reactivity against CYP246 (mean 0.098%±0.080%).

Table 10 shows the sequence of CYP1B1 and the sequences of CYP1B1 peptides that were identified by LPEP analysis as having binding affinity for HLA-A2.

TABLE 10

Identify HLA-A2 Binding Peptide Fragments. CYP1B1

Input Sequence:

MGTSLSPNDPWPLNPLSIQQTTLLLLLSVLATVHVGQRLLRQRRRQLRSAPPGPFAWPLIGNAAA
VGQAAHLSFARLARRYGDVFQIRLGSCPIVVLNGERAIHQALVQQGSAFADRPAFASFRVVSGGR
SMAFGHYSEHWKVQRRAAHSMMRNFFTRQPRSRQVLEGHVLSEARELVALLVRGSADGAFLDP
RPLTVVAVANVMSAVCFGCRYSHDDPEFRELLSHNEEFGRTVGAGSLVDVMPWLQYFPNPVRTV
FREFEQLNRNFSNFILDKFLRHCESLRPGAAPRDMMDAFILSAEKKAAGDSHGGGARLDLENVPA
TITDIFGASQDTLSTALQWLLLLFTRYPDVQTRVQAELDQVVGRDRLPCMGDQPNLPYVLAFLYE
AMRFSSFVPVTIPHATTANTSVLGYHIPKDTVVFVNQWSVNHDPLKWPNPENFDPARFLDKDGLI
NKDLTSRVMIFSVGKRRCIGEELSKMQLFLFISILAHQCDFRANPNEPAKMNFSYGLTIKPKSFKVN
VTLRESMELLDSAVQNLQAKETCQ

Listed below are 9-residue peptides predicted to bind to the HLA-A2 allele with a ln(IC50) < 8. The first entry represents the location in the original sequence of the first amino acid of that peptide. Following the location is the peptide, for which the predicted ln(IC50) is given as the third entry.

22	TLLLLLSVL	7.08
23	LLLLLSVLA	7.71
24	LLLLSVLAT	6.05
25	LLLSVLATV	3.54
55	FAWPLIGNA	5.11
88	RLGSCPIVV	4.61
95	VVLNGERAI	6.58
190	FLDPRPLTV	6.52
200	AVANVMSAV	6.14
239	SLVDVMPWL	2.88
246	WLQYFPNPV	6.23
292	MMDAFILSA	3.31
312	GARLDLENV	7.87
314	RLDLENVPA	6.27
322	ATITDIFGA	6.74
334	TLSTALQWL	6.64
344	LLFTRYPDV	4.69
377	NLPYVLAFL	7.10
380	YVLAFLYEA	1.56
381	VLAFLYEAM	6.09
394	FVPVTIPHA	7.03
419	VVFVNQWSV	7.35
479	QLFLFISIL	5.66
487	LAHQCDFRA	7.54
510	TIKPKSFKV	7.60
528	LLDSAVQNL	4.08

Listed below are 10-residue peptides predicted to bind to the HLA-A2 allele with a ln(IC50) < 8.

4	SLSPNDPWPL	5.26
20	QTTLLLLLSV	6.75
21	TTLLLLLSVL	7.01
22	TLLLLLSVLA	5.18
23	LLLLLSVLAT	7.36
24	LLLLSVLATV	4.55
26	LLSVLATVHV	5.86
88	RLGSCPIVVL	3.08
190	FLDPRPLTVV	7.88
199	VAVANVMSAV	7.87
234	TVGAGSLVDV	7.73

	255	RTVFREFEQL 7.72
	334	TLSTALQWLL 5.85
	336	STALQWLLLL 5.96
	343	LLLFTRYPDV 5.60
5	380	YVLAFLYEAM 5.54
	388	AMRFSSFVPV 7.39
	418	TVVFVNQWSV 6.72
	477	KMQLFLFISI 1.29
	479	QLFLFISILA 3.86
10	486	ILAHQCDFRA 3.87
	494	RANPNEPAKM 7.06
	502	KMNFSYGLTI 7.12

The following Experimental Methods were used to obtain some of the Experimental Results set forth above.

Experimental Methods

Donor and Patient Samples

Peripheral blood from healthy blood donors and cancer patients (Table 2) was obtained by leukapheresis and peripheral blood mononuclear cells (PBMC) were purified by Ficoll-density centrifugation (Schultze *et al.*, J. Clin. Invest. 100:2757-2765, 1997). Primary NHL and AML samples were obtained from discarded specimens. Leukapheresis products and tumor tissue were obtained following informal consent and approval by our institute's Review Board.

Cell Lines

The melanoma cell line K029 was a kind gift of Dr. G. Dranoff (Dana-Farber Cancer Institute, Boston). The fibroblast cell line GM847 was a kind gift of Dr. W. Hahn (Whitehead Institute of Biomedical Research, Cambridge). The 36M ovarian carcinoma cell line was a kind gift of Dr. S. Cannistra (Beth Israel Deaconess Hospital, Boston). The TAP-deficient T2 cell line; the multiple myeloma cell lines U266, IM9, and HS-Sultan; the melanoma cell line SK-MEL-2; and the ovarian carcinoma cell line SK-OV-3 were obtained from the American Type Culture Collection (ATCC; Manassas, VA).

Peptides

The peptides CYP239 (SLVDVMPWL; SEQ ID NO:1) and CYP246 (WLQYFPNPV; SEQ ID NO:2) from CYP1B1, the I540 peptide from hTERT (ILAKFLHWL), the RT-pol476 (ILKEPVHGV) peptide from HIV, the HTLV-TAX11 (LLFGYPVYV), and the peptide F271 (FLWGPRALV) derived from MAGE-3 were purchased from Sigma Genosys Biotechnologies (The Woodlands, TX).

Peptide Prediction

Binding of peptides to HLA molecules can be predicted for the most common HLA alleles by computational methods (Parker *et al.*, J. Immunol. 152:163-75, 1994; Gulukota *et al.*, J. Mol. Biol. 267:1258-67, 1997). To increase specificity of peptide prediction we used two independent algorithms: a matrix algorithm available on the BIMAS (BioInformatics & Molecular Analysis Section at the NIH) web site (Parker *et al.*, J. Immunol. 152:163-75, 1994) and a linear programming algorithm (LPpep) at Boston University (Z. Weng). BIMAS predicts for the half-life of peptides bound to class I molecules, while LPpep predicts an arbitrary half inhibitory concentration (IC_{50}) in competition with a labeled reference peptide. The output value is listed as $\ln(IC_{50})$.

*HLA-A*0201 binding assay*

TAP-deficient T2 cells were pulsed with 40 μg/ml of peptide and 3 μg/ml of β2-microglobulin (Sigma, St. Louis, MO) for 18 hours in serum-free IMDM (Life Technologies, Rockville, MD) at 37°C. Cells were washed three times in serum-free IMDM and HLA-A*0201 expression was measured by flow cytometry using FITC-conjugated mAb BB7.2 (ATCC). Increase of HLA-A2 expression on T2 cells reflects stabilization of MHC complexes by the addition of exogenous peptides and was quantified using the fluorescence index (FI = $(MFI_{\text{peptide pulsed T2}} / MFI_{\text{unpulsed T2}}) - 1$).

Western blot analysis

CYP1B1 expression was determined in microsomal cell fractions. Microsomal protein was isolated by differential speed centrifugation. Cells were harvested, washed, and resuspended in hypotonic buffer. After mechanical homogenization high-density particles were pelleted by centrifugation for 20 minutes at 15,000g. The supernatant was collected and centrifuged for 1 hour at 180,000g. The pellet was resuspended in TEDG buffer, and 100 μg of microsomal protein was separated by SDS-PAGE and transferred to nitrocellulose membrane. Western blot for CYP1B1 was performed according to the manufacturer's recommendations (Gentest, Woburn, MA). Bands were visualized by enhanced chemiluminescent detection (NEN Life Science Products, Boston, MA).

Generation of CTL

CTL were generated as previously described (Vonderheide *et al.*, Immunity 10:673-679,1999), $CD8^+$ T cells (>80% $CD8^+$, >95% $CD3^+$, <2.0% $CD4^+$, and <5% $CD56^+$) were isolated from PBMC by negative selection using magnetic beads. B cells were activated via CD40, and DC were prepared from peripheral blood monocytes with IL-4 and GM-CSF (Schultze *et al.*, J. Clin. Invest. 100:2757-2765, 1997). DC were harvested after 7 days, pulsed with peptide (40 μg/ml) and β2-microglobulin (3 μg/ml) for 2 hr at 37°C, irradiated (33 Gy), and added to autologous $CD8^+$ T cells at a T:DC ratio of 20:1 in RPMI media supplemented with 10% human AB serum, 2 mM glutamine, 15 μg/ml gentamicin, 20 mM HEPES, and 15 ng/ml IL-7 (Endogen, Woburn, MA). At day 7 and weekly thereafter, T cell cultures were harvested and restimulated with irradiated (33 Gy), peptide-pulsed (10 μg/ml) autologous CD40-activated B cells. IL-2 (50 U/ml; Chiron Corp, Emeryville, CA) was introduced on day 8 and replenished as needed every 3–4 days. Flow cytometry was performed as described (Schultze *et al.*, J Clin. Invest. 100:2757-2765, 1997). Assessment of cytotoxic effector function and tetramer analysis were performed with CTL cultures always >90% $CD3^+/CD8^+$, <5% $CD4^+$, and <5% $CD56^+$.

Cytotoxicity Assay

To assess cytolytic function CTL lines were used after at least four antigenic stimulations in standard ^{51}Cr release assays as previously described (Vonderheide *et al.*, Immunity 10:673-679, 1999). Percent specific lysis was calculated from cpm of (experimental result - spontaneous release)/(maximum release - spontaneous release) x100%. Monocytes as targets were isolated from PBMC by RosetteSep® (Stem Cell Technologies, Vancouver) following the manufacturer's recommendations.

Tetramer analysis

Tetrameric A2/peptide complexes with CYP239, CYP246, and TAX11, an immunogenic peptide derived from HTLV-1, were synthesized essentially as described (Altman *et al.*, Science 274: 94-96, 1996) and conjugated to ALEXA-488 (Molecular Probes, Eugene, OR). For staining of CTL lines, cells were incubated with the tetramer and CD8-PE (Beckman Coulter, Fullerton, CA) for 30 minutes at room temperature. Tetramers were also used to sort CYP239-specific CTL. Tetramer sorted CTL were expanded by mitogen stimulation as described (Valmori *et al.*, Cancer Res. 59:2167-2173, 1999).

Use

Use of universal tumor associated antigens in therapeutic methods

As is discussed above, the invention provides methods for preventing or treating conditions associated with excessive cell proliferation and expression of CYP1B1, such as cancer.

Examples of conditions that can be prevented or treated using the methods of the invention, include, for example, all cancers, *e.g.*, melanoma, lymphoma, carcinoma, sarcoma, multiple myeloma, leukemia, lung cancer, ovarian cancer, uterine cancer, cervical cancer, prostate cancer, liver cancer, colon cancer, pancreatic cancer, and brain cancer. Pre-cancerous and non-cancerous conditions characterized by excessive cell proliferation, and expression of a

CYP1B1, can be treated using the methods of the invention as well. For example, all carcinomas *in situ*, *e.g.*, ductal carcinoma *in situ*, lobular carcinoma *in situ*, and cervical carcinoma *in situ*, as well as adenoma and benign polyps can be treated using the methods of the invention.

Patients that can be treated using the methods of the invention include those whose conditions are at early, intermediate, or advanced stages of development. Patients can receive treatment according to the invention before, during, or after other types of treatment, such as chemotherapy, radiation, or surgery, or can receive the treatment of the invention in the absence of any other type of treatment. The methods of the invention can also be used as general prophylactic measures; to prevent conditions from arising in patients that are at risk, or have early signs, of developing a condition associated with excessive cellular proliferation, such as cancer; or to prevent recurrence of such a condition. Additional persons that can be treated, in particular, using vaccination methods of the invention (see below), are those who are to donate cells, such as cytotoxic T lymphocytes, for use in the treatment of another (see below).

Central to the prophylactic and therapeutic methods of the invention is the pathway of cell-mediated immunity involving cytotoxic T lymphocytes (CTLs). In this pathway, an antigen is taken up and processed by an antigen presenting cell, so that a peptide of the antigen is presented on the surface of the cell, in the context of MHC. Such antigen presenting cells then activate cytotoxic T lymphocytes, in an MHC-restricted fashion, to proliferate and kill target cells that express the antigen.

The prophylactic and therapeutic methods of the invention intervene in this pathway at different levels. For example, in one of these methods, a CYP1B1 antigen is administered to a patient, in whom the antigen is taken up by antigen presenting cells, which in turn activate CTLs. In another of these methods, an antigen presenting cell is contacted with a CYP1B1 antigen *ex vivo*, where it takes up, processes, and presents the antigen, in the context of MHC. Such *ex vivo* stimulated APCs are then administered to a patient, in whom they specifically activate CTLs. In yet another of these methods, CTLs are activated *ex vivo* with

APCs presenting CYP1B1 peptides, and the activated CTLs are then administered to a patient. These methods, each of which includes numerous variations, are described in further detail below. Also, it is noted that all of these methods can be carried out with CYP1B1 peptides alone or, preferably, in combination with another (or more) tumor associated antigen polypeptides or peptides (*e.g.*, telomerase).

As is noted above, the prophylactic and therapeutic methods of the invention include one in which CYP1B1, or a fragment thereof that binds to MHC, is administered to a patient, in whom the antigen or fragment is taken up by and processed within an antigen presenting cell, which in turn activates a cytotoxic T cell in the patient. This vaccination method can be carried out using CYP1B1, one or more MHC-binding peptides of CYP1B1, and, in addition to these (or a combination thereof), one or more universal TAAs or one or more MHC-binding peptides of more than one universal TAA, or a combination thereof. Optionally, the antigen can be administered in combination with an adjuvant to enhance the anti-TAA immune response, or the antigen can be packaged into a delivery system (see below).

Any reagent including CYP1B1 or a MHC-binding peptide thereof can be used for vaccination. These include, without limitation, full length CYP1B1, MHC-binding fragments of CYP1B1, as well as fusion proteins including CYP1B1 and MHC-binding fragments thereof. Peptides or polypeptides including CYP1B1 peptides and polypeptides can include 8, 9, 10, 11, 12, or more amino acid stretches having sequence identity with a region of CYP1B1. For example, the peptides can include nine amino acid stretches, in which seven, eight, or all nine of the amino acids in the CYP1B1 peptide nine amino acid sequence are identical to a region of nine amino acids in CYP1B1. In addition, a CYP1B1 peptide or polypeptide can include up to 533 amino acids that are identical to an amino acid sequence found in CYP1B1, for example, 9-20, 20-40, 40-80, 80-200, or 200-533 amino acids that are identical to an amino acid sequence found in CYP1B1. Polypeptides containing CYP1B1 peptides can

contain additional amino acid stretches that do not correspond to the amino acid sequence of CYP1B1.

To vaccinate a patient to elicit a CYP1B1-specific immune response in the patient, it is necessary to obtain large amounts of a CYP1B1 protein or peptide, and this can be accomplished by numerous standard methods, for example, chemical synthesis (*e.g.*, Fmoc methods (Sigma Genosys); see above) or expression in eukaryotic or prokaryotic cells.

Recombinant CYP1B1 peptides can be overexpressed *in vivo* by introducing coding sequences of the peptides into various types of cells, or *in vitro*, using cell-free expression systems that are known in the art. The peptide products can then be purified for generating CYP1B1-specific CTLs *ex vivo* and for vaccine production. Purified CYP1B1 peptides are also useful for diagnostic assays that measure the presence of CYP1B1-specific CTLs in a test sample. For example, the presence (or increased levels) of CYP1B1-specific CTLs in a sample from a subject who has received an anti-CYP1B1 vaccination, relative to the level of CYP1B1-specific CTLs in a reference sample (such as a pre-vaccination sample from the patient), indicates that the patient has mounted a CYP1B1-specific immune response.

CYP1B1 peptides can be produced by chemical synthesis (*e.g.*, by the methods described in *Solid Phase Peptide Synthesis*, 2nd ed., 1984, The Pierce Chemical Co., Rockford, IL, or by other methods known to those skilled in the art of peptide synthesis).

A wide variety of expression systems can be used to produce recombinant CYP1B1 peptides, polypeptides, fragments, fusion proteins, and amino acid sequence variants. CYP1B1 peptides can be produced in prokaryotic hosts (*e.g.*, *E. coli*) or in eukaryotic hosts (*e.g.*, *S. cerevisiae*, insect cells, such as Sf9 cells, or mammalian cells, such as COS-1, NIH 3T3, or HeLa cells). These cells are commercially available from, for example, the American Type Culture Collection, Rockville, Maryland (also see, *e.g.*, Ausubel *et al.*, *Current Protocols in Molecular Biology*, John Wiley & Sons, New York, NY, 1998). The method of transformation and the choice of expression vehicle (*e.g.*, expression vector)

depends on the host system selected. Transformation and transfection methods are described, *e.g.*, by Ausubel *et al.*, *supra*, and expression vehicles can be chosen from the numerous examples that are known in this field.

First, a nucleic acid molecule encoding a CYP1B1 peptide is introduced into a plasmid or other vector, which is then used to transform living cells. Constructs in which a cDNA containing the entire CYP1B1 coding sequence, a fragment of the CYP1B1 coding sequence, amino acid variations of the CYP1B1 coding sequence, or fusion proteins of the aforementioned, inserted in the correct orientation into an expression plasmid, can be used for protein expression. Prokaryotic and eukaryotic expression systems allow various immunogenic domains of CYP1B1 peptides or polypeptides to be recovered as fusion proteins, and then used for the generation of CYP1B1-specific CTLs. In some cases, for example, when a CYP1B1 peptide is to be expressed directly within a patient's cells, it may be desirable to express the CYP1B1 peptide under the control of an inducible or tissue-specific promoter.

Typical expression vectors contain promoters that direct the synthesis of large amounts of mRNA corresponding to the inserted CYP1B1 peptide-encoding nucleic acid molecule in the plasmid-bearing cells. They can also include eukaryotic or prokaryotic "origin of replication" sequences, which allow for their autonomous replication within the host organism, sequences that encode genetic traits that allow vector-containing cells to be selected in the presence of otherwise toxic drugs (such as antibiotics), and sequences that increase the efficiency with which the synthesized mRNA is translated. Stable, long-term vectors can be maintained as freely replicating entities within cells by using regulatory elements of, for example, viruses (*e.g.*, the OriP sequences from the Epstein Barr Virus genome). Cell lines can also be produced that have the vector integrated into genomic DNA, and, in this manner, the gene product is produced on a continuous basis.

Expression of foreign sequences in bacteria such as *Escherichia coli* requires insertion of a nucleic acid molecule encoding a polypeptide into a bacterial expression vector. Plasmid vectors in this category contain several

elements required for propagation of the plasmid in bacteria and expression of inserted DNA of the plasmid by the plasmid-carrying bacteria. Propagation of only plasmid-bearing bacteria is achieved by introducing into the plasmid selectable marker-encoding sequences that allow plasmid-bearing bacteria to grow in the presence of otherwise toxic drugs (*e.g.*, antibiotics). The plasmid also includes a transcriptional promoter that capable of producing large amounts of mRNA from the cloned gene. Such promoters may or may not be inducible promoters. The plasmid also, preferably, contains a polylinker to simplify insertion of the gene in the correct orientation within the vector. For example, in a simple *E. coli* expression vector utilizing the lac promoter, the expression vector plasmid contains a fragment of the *E. coli* chromosome containing the lac promoter and the neighboring *lacZ* gene. In the presence of the lactose analog IPTG, RNA polymerase normally transcribes the *lacZ* gene, producing *lacZ* mRNA, which is translated into the encoded protein, β-galactosidase. The *lacZ* gene can be cut out of the expression vector with restriction endonucleases and replaced by a CYP1B1 peptide gene sequence, or a fragment, fusion, or mutant thereof. When the resulting plasmid is transfected into *E. coli*, addition of IPTG and subsequent transcription from the lac promoter produces mRNA encoding the CYP1B1 polypeptide of interest, which is then translated into a polypeptide.

Once the appropriate expression vector containing a CYP1B1 gene is constructed, it is introduced into an appropriate host cell by transformation, transfection, or transduction techniques that are known in the art, including calcium chloride transformation, calcium phosphate transfection, DEAE-dextran transfection, electroporation, microinjection, protoplast fusion, and liposome-mediated transfection. The host cells that are transformed with the vectors of this invention can include (but are not limited to) *E. coli* or other bacteria, yeast, fungi, insect cells (using, for example, baculoviral vectors for expression), human, mouse, or other animal cells. Mammalian cells can also be used to express CYP1B1 peptides using a vaccinia virus expression system, as is described by Ausubel *et al.*, *supra*.

In vitro expression of CYP1B1 peptides, proteins, fusions, polypeptide fragments, or mutated versions thereof encoded by cloned DNA is also possible using the T7 late promoter expression system. Plasmid vectors containing late promoters and the corresponding RNA polymerases from related bacteriophages such as T3, T5, and SP6 can also be used for *in vitro* production of proteins from cloned DNA. *E. coli* can also be used for expression using an M13 phage such as mGPI-2. Furthermore, vectors that contain phage lambda regulatory sequences, or vectors that direct the expression of fusion proteins, for example, a maltose-binding protein fusion protein or a glutathione-S-transferase fusion protein, also can be used for expression in *E. coli*.

Eukaryotic expression systems permit appropriate post-translational modifications to expressed proteins. Transient transfection of a eukaryotic expression plasmid allows the transient production of CYP1B1 peptides by a transfected host cell. CYP1B1 peptides can also be produced by a stably-transfected mammalian cell line. A number of vectors suitable for stable transfection of mammalian cells are available to the public (*e.g.*, see Pouwels *et al.*, *Cloning Vectors: A Laboratory Manual*, 1985, Supp. 1987), as are methods for constructing such cell lines (see, *e.g.*, Ausubel *et al.*, *supra*). In one example, cDNA encoding a CYP1B1 peptide, protein, fragment, mutant, or fusion protein is cloned into an expression vector that includes the dihydrofolate reductase (DHFR) gene. Integration of the plasmid and, therefore, integration of the CYP1B1 peptide-encoding gene into the host cell chromosome is selected by inclusion of 0.01-300 μM methotrexate in the cell culture medium (as is described by Ausubel *et al.*, *supra*). This dominant selection can be accomplished in most cell types. Recombinant protein expression can be increased by DHFR-mediated amplification of the transfected gene. Methods for selecting cell lines bearing gene amplifications are described by Ausubel *et al.*, *supra*. These methods generally involve extended culture in medium containing gradually increasing levels of methotrexate. The most commonly used DHFR-containing expression vectors are pCVSEII-DHFR and pAdD26SV(A) (described by Ausubel *et al.*, *supra*). The host cells described above or, preferably, a DHFR-deficient CHO

cell line (*e.g.*, CHO DHFR- cells, ATCC Accession No. CRL 9096) are among those most preferred for DHFR selection of a stably-transfected cell line or DHFR-mediated gene amplification. Other drug markers can be analogously used.

Expression of proteins, such as those containing CYP1B1 peptides, in eukaryotic cells allows the production of large amounts of normal or mutant proteins for isolation and purification, and the use of cells expressing a CYP1B1 peptide-containing protein provides a functional assay system for antibodies generated against a CYP1B1 peptide of interest.

Another preferred eukaryotic expression system is the baculovirus system using, for example, the vector pBacPAK9, which is available from Clontech (Palo Alto, CA). If desired, this system can be used in conjunction with other protein expression techniques, for example, the myc tag approach described by Evan *et al.* (Mol. Cell Biol. 5:3610-3616, 1985).

Once a recombinant CYP1B1 protein is expressed, it can be isolated from the expressing cells by cell lysis followed by protein purification techniques, such as affinity chromatography. In this example, an anti-CYP1B1 peptide antibody, which can be produced by methods that are well-known in the art, can be attached to a column and used to isolate recombinant CYP1B1 peptide-containing proteins. Lysis and fractionation of CYP1B1 peptide-harboring cells prior to affinity chromatography can be performed by standard methods (see, *e.g.*, Ausubel *et al.*, *supra*). Once isolated, the recombinant protein can, if desired, be purified further, *e.g.*, by high performance liquid chromatography (HPLC; *e.g.*, see Fisher, *Laboratory Techniques in Biochemistry and Molecular Biology*, Work and Burdon, Eds., Elsevier, 1980).

Preferably, CYP1B1 or a MHC-binding peptide thereof is administered to a patient in association with an adjuvant. For example, a chemical antigen (*e.g.*, Freund's incomplete adjuvant; cytoxan; an aluminum compound, such as aluminum hydroxide, aluminum phosphate, or aluminum hydroxyphosphate; liposomes; ISCOMS; microspheres; protein chochleates; vesicles consisting of nonionic surfactants; cationic amphiphilic dispersions in water; oil/water

emulsions; muramidyldipeptide (MDP) and its derivatives such as glucosyl muramidyldipeptide (GMDP), threonyl-MDP, murametide and murapalmitin; and QuilA and its subfractions; as well as various other compounds such as monophosphoryl-lipid A (MPLA); gamma-inulin; calcitriol; and loxoribine) can be used.

A biological response modifier, which is a soluble mediator that affects induction of an immune response, can also be used as an adjuvant. For example, cytokines (*e.g.*, IL-2 and GM-CSF), chemokines, co-stimulatory molecules (*e.g.*, B7, ICAM, class I monoclonal antibodies, stem cell factor, and stimulated T cells) can be used. Also, bacterial products, such as toxins or, preferably, subunits or fragments thereof that have reduced (if any) toxicity, but maintained adjuvant activity.

Additional types of adjuvant molecules that can be used in the invention include, for example, biological modifiers of the death response (*e.g.*, apoptosis sensitizers) and compounds or treatment that increases the susceptibility of the target cell to treatment, such as radiation and chemotherapy. Also, increasing expression of CYP1B1 in the cell can increase susceptibility of the cell to treatment according to the invention.

Finally, as is described above, cellular adjuvants can be used in the immunization methods of the invention. For example, a CYP1B1 peptide can be administered to a patient on the surface of an antigen presenting cell, in the context of MHC. In additional to professional antigen presenting cells, *e.g.*, dendritic cells, CD40-activated B cells, irradiated tumor cells (*e.g.*, in association with GM-CSF), alternative antigen presenting cells, synthetic antigen presenting cells (*e.g.*, lipid mycels and artificial APC-like scaffolds), and fusions of any of the above-listed cells can be used.

As an alternative to vaccination with a CYP1B1 protein or peptide, vaccination with a nucleic acid molecule that encodes such a protein or peptide can be used for vaccination. Such nucleic acid molecules can be administered as "naked" DNA molecules, present in a plasmid or viral vector, or packaged into a liposome or cell, such as eukaryotic cell, prior to administration. The nucleic acid

molecules can be administered to a patient *in vivo*, or can be used to treat a cell *ex vivo* (*e.g.*, an antigen presenting cell, such as a dendritic cell or a CD40-activated B cell), which is then administered to the patient. Alternatively, RNA, *e.g.*, mRNA, can be used in these methods (see, *e.g.*, Boczkowski *et al.*, J. Exp. Med. 184:465-472, 1996; J. Exp. Med. 186:1177-1182, 1997).

For *in vivo* expression, a gene that encodes a polypeptide that includes CYP1B1 or an MHC-binding peptide thereof must be delivered to cells in a form that can be taken up by the cells, in which a sufficient level of protein is expressed to induce an effective immune response. Retroviral, adenoviral, lentiviral, poxviral, and other viral vectors are suited as nucleic acid expression vectors for *in vivo* delivery, because they show efficient infection and/or integration and expression; see, *e.g.*, Cayouette *et al.*, Hum. Gene Therapy, 8:423-430, 1997; Kido *et al.*, Curr. Eye Res. 15:833-844, 1996; Bloomer *et al.*, J. Virol. 71:6641-6649, 1997; Naldini *et al.*, Science 272:263-267, 1996; Miyoshi *et al.*, Proc. Nat. Acad. Sci., U.S.A., 94:10319-1032, 1997; *Vaccines: New Approaches to Immunological Problems*, R.W. Ellis (Ed.), Butterworth-Heinemann, Boston. For example, any DNA fragment that encodes a polypeptide that contains a CYP1B1 peptide can be cloned into a retroviral vector and transcribed *via* its endogenous promoter, *via* an exogenous promoter, *via* a promoter specific for the target cell type of interest, or, in the case of retroviral vectors, *via* the retroviral long terminal repeat. Other viral vectors that can be used include adenovirus, adeno-associated virus, poxviruses, such as vaccinia virus or bovine papilloma virus, or a herpes virus, such as Epstein-Barr Virus.

Gene transfer *in vivo* can also be achieved by non-viral means. For example, a plasmid vector that encodes a polypeptide that contains a CYP1B1 peptide can be injected directly into skeletal muscle or cardiac muscle by previously described methods (*e.g.*, Wolff *et al.*, Science, 247:1465-1468, 1990). Expression vectors injected into skeletal muscle *in situ* are taken up into muscle cell nuclei and used as templates for expression of their encoded proteins. CYP1B1 peptide-encoding genes that are engineered to contain a signal peptide are secreted from CYP1B1 peptide-expressing muscle cells, after which they

induce an immune response. Gene transfer into cells within the tissues of a living animal also can be achieved by lipofection (Felgner *et al.*, Proc. Natl. Acad. Sci. USA 84:7413, 1987; Ono *et al.*, Neurosci. Lett. 117:259, 1990; Brigham *et al.*, Am. J. Med. Sci. 298:278, 1989; Staubinger *et al.*, Meth. Enz. 101:512, 1983), or asialoorosomucoid-polylysine conjugation (Wu *et al.*, J. Biol. Chem. 263:14621, 1988; Wu *et al.*, J. Biol. Chem. 264:16985, 1989), and analogous methods.

Retroviral vectors, adenoviral vectors, adenovirus-associated viral vectors, or other viral vectors also can be used to deliver genes encoding CYP1B1 peptides or polypeptides to cells *ex vivo*. Numerous vectors useful for this purpose are generally known (see, *e.g.*, Miller, Human Gene Therapy 15-14, 1990; Friedman, Science 244:1275-1281, 1989; Eglitis *et al.*, BioTechniques 6:608-614, 1988; Tolstoshev *et al.*, Curr. Opin. Biotech. 1:55-61, 1990; Sharp, The Lancet 337:1277-1278, 1991; Cornetta *et al.*, Nucl. Acid Res. and Mol. Biol. 36:311-322, 1987; Anderson, Science 226: 401-409, 1984; Moen, Blood Cells 17:407-416, 1991; Miller *et al.*, Biotech. 7:980-990, 1989; Le Gal La Salle *et al.*, Science 259:988-990, 1993; and Johnson, Chest 107:77S-83S, 1995). Retroviral vectors are particularly well developed and have been used in clinical settings (Rosenberg *et al.*, N. Engl. J. Med 323:370, 1990; Anderson *et al.*, U.S. Patent No. 5,399,346).

Gene transfer into cells *ex vivo* can also be achieved by delivery of non-viral vectors, such as expression plasmids, using methods such as calcium phosphate or DEAE dextran transfection, electroporation, and protoplast fusion. Liposomes can also be potentially beneficial for delivery of DNA into a cell.

Cells that are to be transduced or transfected *ex vivo* can be obtained from a patient (*e.g.*, peripheral blood cells, such as B cells or dendritic cells, bone marrow stem cells, or cells from a tumor biopsy) prior to transfection, and re-introduced after transfection. However, the cells also can be derived from a source other than the patient undergoing gene transfer.

In the constructs described above, CYP1B1 peptide expression can be directed from any suitable promoter (*e.g.*, the human cytomegalovirus (CMV), simian virus 40 (SV40), or metallothionein promoters), and regulated by any

appropriate mammalian regulatory element. For example, if desired, enhancers known to preferentially direct gene expression in skeletal muscle cells can be used to direct CYP1B1 peptide expression for vaccination *in situ*. The enhancers used can include, without limitation, those that are characterized as tissue- or cell-specific in their expression.

Conventional pharmaceutical practice can be employed to provide suitable formulations or compositions to administer CYP1B1 peptide or nucleic acid vaccinations for treatment of, or prophylaxis against, cancer. CYP1B1 peptides, CYP1B1 polypeptides, and CYP1B1 nucleic acid molecules can be administered within a pharmaceutically-acceptable diluent, carrier, or excipient, in unit dosage form. Administration can begin before a patient is symptomatic. Any appropriate route of administration can be employed, for example, administration can be parenteral, intravenous, intra-arterial, subcutaneous, intramuscular, intracranial, intraorbital, ophthalmic, intraventricular, intracapsular, intraspinal, intracisternal, intraperitoneal, intranasal, aerosol, by suppositories, or oral administration. Therapeutic formulations can be in the form of liquid solutions or suspensions; for oral administration, formulations can be in the form of tablets or capsules; and for intranasal formulations, in the form of powders, nasal drops, or aerosols. An adjuvant, *e.g.*, as listed above, can be included with the formulation.

Methods well known in the art for making formulations are found, for example, in *Remington's Pharmaceutical Sciences*, (18th edition), ed. A. Gennaro, 1990, Mack Publishing Company, Easton, PA. Formulations for parenteral administration can, for example, contain excipients, sterile water, or saline, polyalkylene glycols such as polyethylene glycol, oils of vegetable origin, or hydrogenated napthalenes. Biocompatible, biodegradable lactide polymer, lactide/glycolide copolymer, or polyoxyethylene-polyoxypropylene copolymers can be used to control the release of the compounds. Other potentially useful parenteral delivery systems for CYP1B1 peptides, polypeptides, and CYP1B1 nucleic acid molecules include ethylene-vinyl acetate copolymer particles, osmotic pumps, implantable infusion systems, and liposomes. Formulations for inhalation can contain excipients, for example, lactose, or can be aqueous

solutions containing, for example, polyoxyethylene-9-lauryl ether, glycocholate and deoxycholate, or can be oily solutions for administration in the form of nasal drops, or as a gel.

As is mentioned above, in addition to the vaccination methods described above, which result in the activation of antigen-specific, MHC-restricted CTLs *in vivo*, such cells (*i.e.*, antigen-specific, MHC-restricted CTLs) can be generated *in vitro*, and then administered to patients. Any cell that expresses an endogenous or exogenously-introduced major histocompatibility antigen-encoding gene can be used to present a CYP1B1 peptide to generate CYP1B1- specific CTLs *in vitro*. In one variation of this approach, a peptide-presenting cell expresses an endogenously or exogenously-introduced CYP1B1 polypeptide-encoding gene. Expression of endogenous CYP1B1 in antigen-presenting cells can be stimulated as described in Schultze *et al.*, *supra*, by cytokines, such as IL-2, or by other molecules that are known to those of skill in this art to stimulate CYP1B1 expression.

In another variation, the antigen presenting cells are pulsed with CYP1B1 or MHC-binding peptide thereof, and the pulsed cells are then used to generate CTLs for administration to a patient. Preferably, the CTLs used in these methods are obtained from the patient to whom they are to ultimately be administered (*i.e.*, the cells are autologous). Alternatively, donor cells (*i.e.*, allogeneic cells) can be used in this method.

Finally, methods in which any of the above-described immunotherapeutic approaches are combined are included in the invention. For example, a patient may be treated with an *ex vivo*, CYP1B1-activated CTL and/or an *ex vivo*, CYP1B1-pulsed APC (*e.g.*, a DC or a CD40-activated B cell), and this treatment can be carried out before, during, or after a vaccination approach (see above). In addition to combining the approaches, each approach (or a combination thereof) can employ multiple peptides of CYP1B1, peptides of other TAAs, or a combination thereof.

Measurement of CYP1B1-specific CTL levels in patients, CTL donors, and CYP1B1-specific CTL preparations generated ex vivo

Patients who have one or more tumors containing CYP1B1-expressing tumor cells and patients who are at risk for developing such tumors can be vaccinated with compositions containing one or more CYP1B1 peptides, CYP1B1 polypeptides, CYP1B1 nucleic acid molecules, cells presenting a CYP1B1 peptide, or mixtures thereof (other TAA (*e.g.*, hTERT) polypeptides, peptides, nucleic acid molecules, or APCs can also be included). Subjects to be used as donors of CYP1B1-specific CTLs for transfer into patients can be similarly vaccinated. Levels of CYP1B1-specific CTLs that result from CYP1B1-specific vaccination of patients or other subjects, or *ex vivo* generation of CYP1B1 specific CTLs, can be monitored using well-known methods. An increase in the level of CYP1B1-specific CTLs in a test sample from a vaccinated subject or a CTL culture stimulated with CYP1B1 *ex vivo*, relative to a reference sample (*e.g.*, a pre-vaccination or pre-stimulation sample), indicates that a CYP1B1-specific CTL response has been stimulated in a vaccinated subject or CYP1B1-stimulated CTL culture. Preferably the increase is by at least 50%, more preferably, at least 100%, still more preferably, at least 200%, and most preferably, at least 400%. In addition, the efficacy of non-antigen-specific immunotherapies (*e.g.*, administration of IL-2 or interferon) against tumors containing CYP1B1-expressing cells can be monitored using similar approaches.

Levels of CYP1B1-specific CTLs can also be assessed in naive subjects who have not received CYP1B1 vaccinations or other treatment for the purpose of generating CYP1B1-specific CTLs. Since some types of tumors (*e.g.*, malignant melanoma, renal cell carcinoma, and non-Hodgkin's lymphoma) themselves elicit immune responses in their hosts, an increase in the level of CYP1B1-specific CTLs cells in a patient sample, compared to the level in a reference sample from a normal subject who does not have a tumor, or in a reference sample that was previously obtained from the patient, can indicate the development of a tumor in a patient not known to have a tumor or an increase in tumor burden (*e.g.*, increased

tumor size, or the development or increase in metastatic tumors) in a patient known to have a tumor.

One approach by which the level of CYP1B1-specific CTLs can be measured is using standard cytotoxicity assays, such as the Cr^{51} release assay (Schultze *et al.*, J. Clin. Invest. 100:2757, 1997), which is described above. Another approach for measuring the level of CYP1B1-specific CTLs involves measuring the binding of peptide-specific CTLs to a tetrameric peptide/MHC complex *in vitro*, as is described by Altman *et al.* (Science 274:94-96, 1996). Briefly, a fusion protein containing an HLA heavy chain molecule, such as HLA-A*0201, plus a peptide that is a substrate for biotinylation at the C-terminus of the HLA polypeptide, is produced. The fusion protein is folded *in vitro* in the presence 2-microglobulin and a CYP1B1 peptide ligand. The purified MHC/CYP1B1 peptide complexes are then biotinylated at the C-terminus of the HLA heavy chain, and tetramers are produced by mixing the biotinylated MHC/CYP1B1 peptide complexes with phycoerythrin-labeled deglycosylated avidin at a molar ratio of 4:1. Samples that contain CTLs (such as blood samples or *ex vivo* cultures) are mixed with the CYP1B1 peptide/MHC tetrameric complexes and the relative amount of CYP1B1-specific CTLs that bind to the CYP1B1 peptide/MHC tetrameric complexes can be measured for each sample by flow cytometry, using methods described by Altman *et al.*, *supra*, and by other methods known to those of skill in this art. Another method that can be used is ELISPOT (Herr *et al.*, J. Immunol. Methods 203:141-152, 1997).

Other Embodiments

All publications and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each independent publication or patent application was specifically and individually indicated to be incorporated by reference.

While the invention has been described in connection with specific embodiments thereof, it will be understood that it is capable of further modifications, and this application is intended to cover any variations, uses, or

adaptations of the invention following, in general, the principles of the invention and including such departures from the present disclosure come within known or customary practice within the art to which the invention pertains and can be applied to the essential features hereinbefore set forth, and follows in the scope of the appended claims.

What is claimed is:

APPENDIX A

Search Report

HLA-A*0201 Nonamers

HLA-A*0201 Decamers

HLA-A*0201 Octamers

HLA-A*0202 Nonamers

HLA-A*0202 Decamers

HLA-A*0203 Nonamers

HLA-A*0203 Decamers

HLA-A*0203 Octamers
HLA-A1 Nonamers
HLA-A1 Decamers
HLA-A26 Nonamers
HLA-A26 Decamers

HLA-B*0702 Nonamers

HLA-B*0702 Decamers

HLA-B*1510 Nonamers

HLA-B*2705 Nonamers
HLA-B8 Octamers
HLA-B8 Nonamers

HLA-A*0201 Nonamers

Pos	1 2 3 4 5 6 7 8 9
25	L L L S V L A T V
22	T L L L L L S V L
528	L L D S A V Q N L
479	Q L F L F I S I L
190	F L D P R P L T V
377	N L P Y V L A F L
344	L L F T R Y P D V
334	T L S T A L Q W L
239	S L V D V M P W L
58	P L I G N A A A V
24	L L L L S V L A T
21	T T L L L L L S V
170	V L S E A R E L V
17	S I Q Q T T L L L
521	T L R E S M E L L
510	T I K P K S F K V
196	L T V V A V A N V
76	R L A R R Y G D V

HLA-A1 Nonamers

Pos	1 2 3 4 5 6 7 8 9
372	M G D Q P N L P Y
241	V D V M P W L Q Y
404	T A N T S V L G Y
190	F L D P R P L T V
185	S A D G A F L D P
174	A R E L V A L L V
171	L S E A R E L V A
165	V L E G H V L S E
7	P N D P W P L N P
445	F L D K D G L I N
341	W L L L L F T R Y
522	L R E S M E L L D
336	S T A L Q W L L L
218	D P E F R E L L S
206	S A V C F G C R Y
129	G R S M A F G H Y
439	N F D P A R F L D
378	L P Y V L A F L Y

HLA-B*0702 Nonamers

Pos	1 2 3 4 5 6 7 8 9
192	D P R P L T V V A
51	P P G P F A W P L
414	I P K D T V V F V
375	Q P N L P Y V L A
288	A P R D M M D A F
399	I P H A T T A N T
250	F P N P V R T V F
194	R P L T V V A V A
512	K P K S F K V N V
50	A P P G P F A W P
320	V P A T I T D I F
117	R P A F A S F R V
89	L G S C P I V V L
57	W P L I G N A A A
474	E L S K M Q L F L
395	V P V T I P H A T
183	R G S A D G A F L
309	H G G G A R L D L

HLA-B*2705 Nonamers

Pos	1 2 3 4 5 6 7 8 9
232	G R T V G A G S L
37	Q R L L R Q R R R
443	A R F L D K D G L
258	F R E F E Q L N R
145	R R A A H S M M R
79	R R Y G D V F Q I
347	T R Y P D V Q T R
467	K R R C I G E E L
265	N R N F S N F I L
116	D R P A F A S F R
514	K S F K V N V T L
469	R C I G E E L S K
182	V R G S A D G A F
129	G R S M A F G H Y
47	L R S A P P G P F
40	L R Q R R R Q L R
175	R E L V A L L V R
144	Q R R A A H S M M

39 LLRQRRRQL	324 ITDIFGASQ	14 NPLSIQQTT	479 QLFLFISIL
525 SMELLDSAV	258 FREFEQLNR	438 ENFDPARFL	472 GEELSKMQL
337 TALQWLLLL	216 HDDPEFREL	402 ATTANTSVL	383 AFLYEAMRF
246 WLQYFPNPV	73 SFARLARRY	173 EARELVALL	295 AFILSAEKK
235 VGAGSLVDV	499 EPAKMNFSY	64 AAVGQAAHL	289 PRDMMDAFI
172 SEARELVAL	292 MMDAFILSA	48 RSAPPGPFA	163 RQVLEGHVL
23 LLLLLSVLA	137 YSEHWKVQR	514 KSFKVNVTL	43 RRRQLRSAP
470 CIGEELSKM	81 YGDVFQIRL	467 KRRCIGEEL	509 LTIKPKSFK
380 YVLAFLYEA	349 YPDVQTRVQ	370 PCMGDQPNL	370 PCMGDQPNL
316 DLENVPATI	497 PNEPAKMNF	307 DSHGGGARL	307 DSHGGGARL
292 MMDAFILSA	428 NHDPLKWPN	172 SEARELVAL	294 DAFILSAEK
173 EARELVALL	415 PKDTVVFVN	159 QPRSRQVLE	213 RYSHDDPEF
88 RLGSCPIVV	359 ELDQVVGRD	99 GERAIHQAL	188 GAFLDPRPL
64 AAVGQAAHL	228 NEEFGRTVG	69 AAHLSFARL	153 RNFFTRQPR
520 VTLRESMEL	20 QTTLLLLLS	8 NDPWPLNPL	87 IRLGSCPIV
336 STALQWLLL	530 DSAVQNLQA	6 SPNDPWPLN	72 LSFARLARR
312 GARLDLENV	447 DKDGLINKD	501 AKMNFSYGL	44 RRQLRSAPP
249 YFPNPVRTV	316 DLENVPATI	499 EPAKMNFSY	36 GQRLLRQRR
200 AVANVMSAV	215 SHDDPEFRE	496 NPNEPAKMN	22 TLLLLLSVL
165 VLEGHVLSE	33 VHVGQRLLR	424 QWSVNHDPL	520 VTLRESMEL
89 LGSCPIVVL	528 LLDSAVQNL	349 YPDVQTRVQ	494 RANPNEPAK
15 PLSIQQTTL	525 SMELLDSAV	346 FTRYPDVQT	481 FLFISILAH
481 FLFISILAH	505 FSYGLTIKP	336 STALQWLLL	468 RRCIGEELS
474 ELSKMQLFL	456 LTSRVMIFS	331 SQDTLSTAL	461 MIFSVGKRR
419 VVFVNQWSV	393 SFVPVTIPH	327 IFGASQDTL	460 VMIFSVGKR
414 IPKDTVVFV	376 PNLPYVLAF	284 RPGAAPRDM	459 RVMIFSVGK
381 VLAFLYEAM	333 DTLSTALQW	216 HDDPEFREL	451 LINKDLTSR
373 GDQPNLPYV	331 SQDTLSTAL	189 AFLDPRPLT	446 LDKDGLINK
355 RVQAELDQV	314 RLDLENVPA	163 RQVLEGHVL	341 WLLLLFTRY
338 ALQWLLLLF	305 AGDSHGGGA	158 RQPRSRQVL	340 QWLLLLFTR
282 SLRPGAAPR	299 SAEKKAAGD	115 ADRPAFASF	337 TALQWLLLL
169 HVLSEAREL	240 LVDVMPWLQ	53 GPFAWPLIG	313 ARLDLENVP
95 VVLNGERAI	114 FADRPAFAS	47 LRSAPPGPF	283 LRPGAAPRD
86 QIRLGSCPI	21 TTLLLLLSV	39 LLRQRRRQL	260 EFEQLNRNF
69 AAHLSFARL	476 SKMQLFLFI	31 ATVHVGQRL	247 LQYFPNPVR
451 LINKDLTSR	471 IGEELSKMQ	18 IQQTTLLLL	161 RSRQVLEGH
450 GLINKDLTS	453 NKDLTSRVM	17 SIQQTTLLL	158 RQPRSRQVL
412 YHIPKDTVV	397 VTIPHATTA	15 PLSIQQTTL	124 RVVSGGRSM
409 VLGYHIPKD	385 LYEAMRFSS	11 WPLNPLSIQ	89 LGSCPIVVL
402 ATTANTSVL	365 GRDRLPCMG	528 LLDSAVQNL	69 AAHLSFARL
342 LLLLFTRYP	357 QAELDQVVG	521 TLRESMELL	64 AAVGQAAHL
322 ATITDIFGA	279 HCESLRPGA	448 KDGLINKDL	16 LSIQQTTLL
272 ILDKFLRHC	272 ILDKFLRHC	443 ARFLDKDGL	508 GLTIKPKSF
191 LDPRPLTVV	260 EFEQLNRNF	436 NPENFDPAR	504 NFSYGLTIK
87 IRLGSCPIV	227 HNEEFGRTV	430 DPLKWPNPE	497 PNEPAKMNF
55 FAWPLIGNA	221 FRELLSHNE	390 RFSSFVPVT	474 ELSKMQLFL
18 IQQTTLLLL	91 SCPIVVLNG	377 NLPYVLAFL	448 KDGLINKDL
514 KSFKVNVTL	90 GSCPIVVLN	337 TALQWLLLL	438 ENFDPARFL
501 AKMNFSYGL	490 QCDFRANPN	334 TLSTALQWL	408 SVLGYHIPK
460 VMIFSVGKR	472 GEELSKMQL	290 RDMMDAFIL	389 MRFSSFVPV
457 TSRVMIFSV	440 FDPARFLDK	229 EEFGRTVGA	382 LAFLYEAMR
356 VQAELDQVV	436 NPENFDPAR	218 DPEFRELLS	376 PNLPYVLAF
319 NVPATITDI	426 SVNHDPLKW	148 AHSMMRNFF	361 DQVVGRDRL
315 LDLENVPAT	353 QTRVQAELD	19 QQTTLLLLL	358 AELDQVVGR
314 RLDLENVPA	338 ALQWLLLLF	16 LSIQQTTLL	352 VQTRVQAEL
297 ILSAEKKAA	289 PRDMMDAFI	9 DPWPLNPLS	327 IFGASQDTL
296 FILSAEKKA	271 FILDKFLRH	493 FRANPNEPA	306 GDSHGGGAR
233 RTVGAGSLV	233 RTVGAGSLV	476 SKMQLFLFI	290 RDMMDAFIL
188 GAFLDPRPL	98 NGERAIHQA	441 DPARFLDKD	282 SLRPGAAPR

180 LLVRGSADG	48 RSAPPGPFA	434 WPNPENFDP	277 LRHCESLRP
131 SMAFGHYSE	31 ATVHVGQRL	413 HIPKDTVVF	275 KFLRHCESL
102 AIHQALVQQ	17 SIQQTTLLL	376 PNLPYVLAF	269 SNFILDKFL
96 VLNGERAIH	516 FKVNVTLRE	374 DQPNLPYVL	256 TVFREFEQL
32 TVHVGQRLL	379 PYVLAFLYE	369 LPCMGDQPN	250 FPNPVRTVF
31 ATVHVGQRL	291 DMMDAFILS	361 DQVVGRDRL	221 FRELLSHNE
29 VLATVHVGQ	282 SLRPGAAPR	352 VQTRVQAEL	219 PEFRELLSH
27 LSVLATVHV	266 RNFSNFILD	335 LSTALQWLL	208 VCFGCRYSH
16 LSIQQTTLL	250 FPNPVRTVF	329 GASQDTLST	202 ANVMSAVCF
8 NDPWPLNPL	234 TVGAGSLVD	314 RLDLENVPA	183 RGSADGAFL
452 INKDLTSRV	160 PRSRQVLEG	297 ILSAEKKAA	174 ARELVALLV
401 HATTANTSV	156 FTRQPRSRQ	275 KFLRHCESL	169 HVLSEAREL
397 VTIPHATTA	101 RAIHQALVQ	269 SNFILDKFL	132 MAFGHYSEH
307 DSHGGGARL	12 PLNPLSIQQ	256 TVFREFEQL	106 ALVQQGSAF
275 KFLRHCESL	503 MNFSYGLTI	252 NPVRTVFRE	81 YGDVFQIRL
256 TVFREFEQL	481 FLFISILAH	244 MPWLQYFPN	80 RYGDVFQIR
199 VAVANVMSA	475 LSKMQLFLF	239 SLVDVMPWL	78 ARRYGDVFQ
179 ALLVRGSAD	408 SVLGYHIPK	235 VGAGSLVDV	31 ATVHVGQRL
79 RRYGDVFQI	403 TTANTSVLG	217 DDPEFRELL	15 PLSIQQTTL
19 QQTTLLLLL	402 ATTANTSVL	191 LDPRPLTVV	531 SAVQNLQAK
4 SLSPNDPWP	392 SSFVPVTIP	188 GAFLDPRPL	506 SYGLTIKPK
486 ILAHQCDFR	363 VVGRDRLPC	125 VVSGGRSMA	485 SILAHQCDF
477 KMQLFLFIS	346 FTRYPDVQT	113 AFADRPAFA	470 CIGEELSKM
443 ARFLDKDGL	337 TALQWLLLL	81 YGDVFQIRL	458 SRVMIFSVG
411 GYHIPKDTV	318 ENVPATITD	22 TLLLLLSVL	444 RFLDKDGLI
406 NTSVLGYHI	309 HGGGARLDL	5 LSPNDPWPL	421 FVNQWSVNH
394 FVPVTIPHA	307 DSHGGGARL	520 VTLRESMEL	413 HIPKDTVVF
384 FLYEAMRFS	184 GSADGAFLD	513 PKSFKVNVT	365 GRDRLPCMG
352 VQTRVQAEL	121 ASFRVVSGG	479 QLFLFISIL	354 TRVQAELDQ
343 LLLFTRYPD	115 ADRPAFASF	472 GEELSKMQL	338 ALQWLLLLF
331 SQDTLSTAL	71 HLSFARLAR	454 KDLTSRVMI	335 LSTALQWLL
329 GASQDTLST	49 SAPPGPFAW	396 PVTIPHATT	331 SQDTLSTAL
327 IFGASQDTL	24 LLLLSVLAT	391 FSSFVPVTI	271 FILDKFLRH
326 DIFGASQDT	19 QQTTLLLLL	389 MRFSSFVPV	270 NFILDKFLR
271 FILDKFLRH	18 IQQTTLLLL	378 LPYVLAFLY	268 FSNFILDKF
236 GAGSLVDVM	16 LSIQQTTLL	338 ALQWLLLLF	267 NFSNFILDK
232 GRTVGAGSL	520 VTLRESMEL	317 LENVPATIT	236 GAGSLVDVM
227 HNEEFGRTV	514 KSFKVNVTL	305 AGDSHGGGA	223 ELLSHNEEF
216 HDDPEFREL	509 LTIKPKSFK	292 MMDAFILSA	173 EARELVALL
193 PRPLTVVAV	478 MQLFLFISI	265 NRNFSNFIL	138 SEHWKVQRR
177 LVALLVRGS	474 ELSKMQLFL	249 YFPNPVRTV	126 VSGGRSMAF
176 ELVALLVRG	469 RCIGEELSK	233 RTVGAGSLV	123 FRVVSGGRS
135 GHYSEHWKV	463 FSVGKRRCI	232 GRTVGAGSL	115 ADRPAFASF
107 LVQQGSAFA	450 GLINKDLTS	213 RYSHDDPEF	112 SAFADRPAF
512 KPKSFKVNV	417 DTVVFVNQW	202 ANVMSAVCF	99 GERAIHQAL
503 MNFSYGLTI	412 YHIPKDTVV	200 AVANVMSAV	93 PIVVLNGER
502 KMNFSYGLT	406 NTSVLGYHI	193 PRPLTVVAV	75 ARLARRYGD
476 SKMQLFLFI	391 FSSFVPVTI	190 FLDPRPLTV	63 AAAVGQAAH
467 KRRCIGEEL	322 ATITDIFGA	181 LVRGSADGA	33 VHVGQRLLR
454 KDLTSRVMI	308 SHGGGARLD	174 ARELVALLV	32 TVHVGQRLL
389 MRFSSFVPV	268 FSNFILDKF	171 LSEARELVA	528 LLDSAVQNL
387 EAMRFSSFV	205 MSAVCFGCR	169 HVLSEAREL	515 SFKVNVTLR
341 WLLLLFTRY	196 LTVVAVANV	126 VSGGRSMAF	501 AKMNFSYGL
339 LQWLLLLFT	175 RELVALLVR	112 SAFADRPAF	495 ANPNEPAKM
330 ASQDTLSTA	83 DVFQIRLGS	106 ALVQQGSAF	473 EELSKMQLF
309 HGGGARLDL	66 VGQAAHLSF	92 CPIVVLNGE	437 PENFDPARF
269 SNFILDKFL	9 DPWPLNPLS	87 IRLGSCPIV	432 LKWPNPENF
181 LVRGSADGA	4 SLSPNDPWP	79 RRYGDVFQI	425 WSVNHDPLK
178 VALLVRGSA	523 RESMELLDS	77 LARRYGDVF	402 ATTANTSVL

162 SRQVLEGHV	510 TIKPKSFKV	62 NAAAVGQAA	377 NLPYVLAFL
150 SMMRNFFTR	480 LFLFISILA	58 PLIGNAAAV	374 DQPNLPYVL
125 VVSGGRSMA	458 SRVMIFSVG	56 AWPLIGNAA	372 MGDQPNLPY
106 ALVQQGSAF	446 LDKDGLINK	32 TVHVGQRLL	367 DRLPCMGDQ
81 YGDVFQIRL	425 WSVNHDPLK	24 LLLLSVLAT	309 HGGGARLDL
63 AAAVGQAAH	407 TSVLGYHIP	530 DSAVQNLQA	263 QLNRNFSNF
28 SVLATVHVG	354 TRVQAELDQ	503 MNFSYGLTI	239 SLVDVMPWL
26 LLSVLATVH	339 LQWLLLLFT	463 FSVGKRRCI	216 HDDPEFREL
527 ELLDSAVQN	335 LSTALQWLL	412 YHIPKDTVV	212 CRYSHDDPE
517 KVNVTLRES	329 GASQDTLST	411 GYHIPKDTV	197 TVVAVANVM
508 GLTIKPKSF	311 GGARLDLEN	406 NTSVLGYHI	193 PRPLTVVAV
485 SILAHQCDF	281 ESLRPGAAP	387 EAMRFSSFV	172 SEARELVAL
478 MQLFLFISI	277 LRHCESLRP	350 PDVQTRVQA	160 PRSRQVLEG
463 FSVGKRRCI	267 NFSNFILDK	339 LQWLLLLFT	157 TRQPRSRQV
455 DLTSRVMIF	255 RTVFREFEQ	315 LDLENVPAT	147 AAHSMMRNF
445 FLDKDGLIN	219 PEFRELLSH	289 PRDMMDAFI	137 YSEHWKVQR
444 RFLDKDGLI	214 YSHDDPEFR	280 CESLRPGAA	100 ERAIHQALV
413 HIPKDTVVF	161 RSRQVLEGH	264 LNRNFSNFI	51 PPGPFAWPL
391 FSSFVPVTI	126 VSGGRSMAF	253 PVRTVFREF	39 LLRQRRRQL
358 AELDQVVGR	125 VVSGGRSMA	248 QYFPNPVRT	35 VGQRLLRQR
335 LSTALQWLL	88 RLGSCPIVV	170 VLSEARELV	26 LLSVLATVH
264 LNRNFSNFI	53 GPFAWPLIG	118 PAFASFRVV	19 QQTTLLLLL
224 LLSHNEEFG	50 APPGPFAWP	100 ERAIHQALV	18 IQQTTLLLL
217 DDPEFRELL	41 RQRRRQLRS	88 RLGSCPIVV	17 SIQQTTLLL
194 RPLTVVAVA	34 HVGQRLLRQ	86 QIRLGSCPI	8 NDPWPLNPL
183 RGSADGAFL	10 PWPLNPLSI	67 GQAAHLSFA	521 TLRESMELL
174 ARELVALLV	3 TSLSPNDPW	66 VGQAAHLSF	499 EPAKMNFSY
166 LEGHVLSEA	2 GTSLSPNDP	61 GNAAAVGQA	493 FRANPNEPA
164 QVLEGHVLS	515 SFKVNVTLR	27 LSVLATVHV	455 DLTSRVMIF
157 TRQPRSRQV	465 VGKRRCIGE	524 ESMELLDSA	454 KDLTSRVMI
124 RVVSGGRSM	434 WPNPENFDP	457 TSRVMIFSV	436 NPENFDPAR
120 FASFRVVSG	416 KDTVVFVNQ	452 INKDLTSRV	393 SFVPVTIPH
118 PAFASFRVV	386 YEAMRFSSF	435 PNPENFDPA	386 YEAMRFSSF
105 QALVQQGSA	347 TRYPDVQTR	397 VTIPHATTA	378 LPYVLAFLY
99 GERAIHQAL	330 ASQDTLSTA	386 YEAMRFSSF	336 STALQWLLL
59 LIGNAAAVG	328 FGASQDTLS	383 AFLYEAMRF	284 RPGAAPRDM
46 QLRSAPPGP	286 GAAPRDMMD	373 GDQPNLPYV	259 REFEQLNRN
38 RLLRQRRRQ	253 PVRTVFREF	356 VQAELDQVV	253 PVRTVFREF
5 LSPNDPWPL	239 SLVDVMPWL	355 RVQAELDQV	242 DVMPWLQYF
535 NLQAKETCQ	238 GSLVDVMPW	348 RYPDVQTRV	241 VDVMPWLQY
532 AVQNLQAKE	226 SHNEEFGRT	330 ASQDTLSTA	186 ADGAFLDPR
531 SAVQNLQAK	192 DPRPLTVVA	326 DIFGASQDT	167 EGHVLSEAR
524 ESMELLDSA	189 AFLDPRPLT	322 ATITDIFGA	148 AHSMMRNFF
483 FISILAHQC	170 VLSEARELV	319 NVPATITDI	141 WKVQRRAAH
408 SVLGYHIPK	150 SMMRNFFTR	312 GARLDLENV	128 GGRSMAFGH
404 TANTSVLGY	149 HSMMRNFFT	287 AAPRDMMDA	122 SFRVVSGGR
398 TIPHATTAN	130 RSMAFGHYS	279 HCESLRPGA	96 VLNGERAIH
374 DQPNLPYVL	106 ALVQQGSAF	242 DVMPWLQYF	73 SFARLARRY
370 PCMGDQPNL	80 RYGDVFQIR	199 VAVANVMSA	68 QAAHLSFAR
364 VGRDRLPCM	55 FAWPLIGNA	196 LTVVAVANV	66 VGQAAHLSF
361 DQVVGRDRL	54 PFAWPLIGN	182 VRGSADGAF	42 QRRRQLRSA
359 ELDQVVGRD	6 SPNDPWPLN	149 HSMMRNFFT	30 LATVHVGQR
348 RYPDVQTRV	529 LDSAVQNLQ	147 AAHSMMRNF	522 LRESMELLD
346 FTRYPDVQT	524 ESMELLDSA	140 HWKVQRRAA	518 VNVTLRESM
324 ITDIFGASQ	511 IKPKSFKVN	139 EHWKVQRRA	503 MNFSYGLTI
303 KAAGDSHGG	507 YGLTIKPKS	111 GSAFADRPA	486 ILAHQCDFR
290 RDMMDAFIL	494 RANPNEPAK	107 LVQQGSAFA	478 MQLFLFISI
276 FLRHCESLR	488 AHQCDFRAN	94 IVVLNGERA	475 LSKMQLFLF
263 QLNRNFSNF	484 ISILAHQCD	76 RLARRYGDV	453 NKDLTSRVM

243 VMPWLQYFP	468 RRCIGEELS	70 AHLSFARLA	440 FDPARFLDK
223 ELLSHNEEF	460 VMIFSVGKR	42 QRRRQLRSA	405 ANTSVLGYH
189 AFLDPRPLT	457 TSRVMIFSV	23 LLLLLSVLA	404 TANTSVLGY
163 RQVLEGHVL	432 LKWPNPENF	21 TTLLLLLSV	360 LDQVVGRDR
117 RPAFASFRV	420 VFVNQWSVN	10 PWPLNPLSI	348 RYPDVQTRV
113 AFADRPAFA	409 VLGYHIPKD	525 SMELLDSAV	334 TLSTALQWL
100 ERAIHQALV	373 GDQPNLPYV	510 TIKPKSFKV	320 VPATITDIF
71 HLSFARLAR	371 CMGDQPNLP	502 KMNFSYGLT	319 NVPATITDI
67 GQAAHLSFA	367 DRLPCMGDQ	497 PNEPAKMNF	288 APRDMMDAF
62 NAAAVGQAA	358 AELDQVVGR	485 SILAHQCDF	276 FLRHCESLR
61 GNAAAVGQA	321 PATITDIFG	478 MQLFLFISI	251 PNPVRTVFR
57 WPLIGNAAA	298 LSAEKKAAG	473 EELSKMQLF	225 LSHNEEFGR
49 SAPPGPFAW	276 FLRHCESLR	455 DLTSRVMIF	217 DDPEFRELL
12 PLNPLSIQQ	263 QLNRNFSNF	444 RFLDKDGLI	206 SAVCFGCRY
495 ANPNEPAKM	249 YFPNPVRTV	437 PENFDPARF	162 SRQVLEGHV
487 LAHQCDFRA	248 QYFPNPVRT	432 LKWPNPENF	155 FFTRQPRSR
482 LFISILAHQ	245 PWLQYFPNP	401 HATTANTSV	152 MRNFFTRQP
472 GEELSKMQL	242 DVMPWLQYF	394 FVPVTIPHA	150 SMMRNFFTR
448 KDGLINKDL	237 AGSLVDVMP	380 YVLAFLYEA	134 FGHYSEHWK
438 ENFDPARFL	231 FGRTVGAGS	372 MGDQPNLPY	109 QQGSAFADR
431 PLKWPNPEN	225 LSHNEEFGR	344 LLFTRYPDV	77 LARRYGDVF
426 SVNHDPLKW	194 RPLTVVAVA	316 DLENVPATI	71 HLSFARLAR
424 QWSVNHDPL	178 VALLVRGSA	281 ESLRPGAAP	5 LSPNDPWPL
399 IPHATTANT	164 QVLEGHVLS	263 QLNRNFSNF	476 SKMQLFLFI
390 RFSSFVPVT	157 TRQPRSRQV	260 EFEQLNRNF	463 FSVGKRRCI
382 LAFLYEAMR	131 SMAFGHYSE	246 WLQYFPNPV	424 QWSVNHDPL
371 CMGDQPNLP	122 SFRVVSGGR	227 HNEEFGRTV	364 VGRDRLPCM
368 RLPCMGDQP	118 PAFASFRVV	226 SHNEEFGRT	254 VRTVFREFE
298 LSAEKKAAG	111 GSAFADRPA	223 ELLSHNEEF	222 RELLSHNEE
287 AAPRDMMDA	97 LNGERAIHQ	178 VALLVRGSA	214 YSHDDPEFR
265 NRNFSNFIL	96 VLNGERAIH	166 LEGHVLSEA	205 MSAVCFGCR
242 DVMPWLQYF	82 GDVFQIRLG	157 TRQPRSRQV	194 RPLTVVAVA
204 VMSAVCFGC	72 LSFARLARR	119 AFASFRVVS	143 VQRRAAHSM
192 DPRPLTVVA	69 AAHLSFARL	95 VVLNGERAI	95 VVLNGERAI
158 RQPRSRQVL	64 AAVGQAAHL	78 ARRYGDVFQ	86 QIRLGSCPI
94 IVVLNGERA	51 PPGPFAWPL	55 FAWPLIGNA	450 GLINKDLTS
51 PPGPFAWPL	38 RLLRQRRRQ	52 PGPFAWPLI	447 DKDGLINKD
48 RSAPPGPFA	32 TVHVGQRLL	25 LLLSVLATV	391 FSSFVPVTI
42 QRRRQLRSA	29 VLATVHVGQ	533 VQNLQAKET	381 VLAFLYEAM
13 LNPLSIQQT	28 SVLATVHVG	508 GLTIKPKSF	316 DLENVPATI
509 LTIKPKSFK	27 LSVLATVHV	487 LAHQCDFRA	301 EKKAAGDSH
505 FSYGLTIKP	5 LSPNDPWPL	480 LFLFISILA	285 PGAAPRDMM
494 RANPNEPAK	533 VQNLQAKET	475 LSKMQLFLF	168 GHVLSEARE
459 RVMIFSVGK	532 AVQNLQAKE	449 DGLINKDLT	135 GHYSEHWKV
447 DKDGLINKD	521 TLRESMELL	419 VVFVNQWSV	101 RAIHQALVQ
417 DTVVFVNQW	500 PAKMNFSYG	410 LGYHIPKDT	45 RQLRSAPPG
396 PVTIPHATT	495 ANPNEPAKM	366 RDRLPCMGD	41 RQRRRQLRS
388 AMRFSSFVP	493 FRANPNEPA	296 FILSAEKKA	10 PWPLNPLSI
347 TRYPDVQTR	486 ILAHQCDFR	285 PGAAPRDMM	505 FSYGLTIKP
340 QWLLLLFTR	464 SVGKRRCIG	268 FSNFILDKF	412 YHIPKDTVV
323 TITDIFGAS	461 MIFSVGKRR	237 AGSLVDVMP	406 NTSVLGYHI
299 SAEKKAAGD	435 PNPENFDPA	185 SADGAFLDP	314 RLDLENVPA
294 DAFILSAEK	431 PLKWPNPEN	162 SRQVLEGHV	266 RNFSNFILD
291 DMMDAFILS	423 NQWSVNHDP	156 FTRQPRSRQ	264 LNRNFSNFI
286 GAAPRDMMD	418 TVVFVNQWS	135 GHYSEHWKV	233 RTVGAGSLV
248 QYFPNPVRT	405 ANTSVLGYH	105 QALVQQGSA	154 NFFTRQPRS
229 EEFGRTVGA	389 MRFSSFVPV	98 NGERAIHQA	146 RAAHSMMRN
226 SHNEEFGRT	377 NLPYVLAFL	71 HLSFARLAR	38 RLLRQRRRQ
203 NVMSAVCFG	375 QPNLPYVLA	13 LNPLSIQQT	532 AVQNLQAKE

198 VVAVANVMS
197 TVVAVANVM
195 PLTVVAVAN
185 SADGAFLDP
151 MMRNFFTRQ
132 MAFGHYSEH
112 SAFADRPAF
90 GSCPIVVLN
72 LSFARLARR
70 AHLSFARLA
34 HVGQRLLRQ
30 LATVHVGQR
20 QTTLLLLLS
518 VNVTLRESM
493 FRANPNEPA
461 MIFSVGKRR
446 LDKDGLINK
441 DPARFLDKD
421 FVNQWSVNH
403 TTANTSVLG
392 SSFVPVTIP
376 PNLPYVLAF
375 QPNLPYVLA
351 DVQTRVQAE
317 LENVPATIT
304 AAGDSHGGG
259 REFEQLNRN
201 VANVMSAVC
143 VQRRAAHSM
121 ASFRVVSGG
115 ADRPAFASF
98 NGERAIHQA
93 PIVVLNGER
92 CPIVVLNGE
68 QAAHLSFAR
56 AWPLIGNAA
14 NPLSIQQTT
10 PWPLNPLSI
533 VQNLQAKET
507 YGLTIKPKS
480 LFLFISILA
469 RCIGEELSK
466 GKRRCIGEE
395 VPVTIPHAT
313 ARLDLENVP
311 GGARLDLEN
305 AGDSHGGGA
289 PRDMMDAFI
268 FSNFILDKF
238 GSLVDVMPW
234 TVGAGSLVD
208 VCFGCRYSH
207 AVCFGCRYS
206 SAVCFGCRY
186 ADGAFLDPR
175 RELVALLVR
142 KVQRRAAHS
138 SEHWKVQRR
119 AFASFRVVS

362 QVVGRDRLP
361 DQVVGRDRL
360 LDQVVGRDR
352 VQTRVQAEL
323 TITDIFGAS
306 GDSHGGGAR
296 FILSAEKKA
295 AFILSAEKK
285 PGAAPRDMM
257 VFREFEQLN
256 TVFREFEQL
247 LQYFPNPVR
217 DDPEFRELL
208 VCFGCRYSH
207 AVCFGCRYS
204 VMSAVCFGC
200 AVANVMSAV
198 VVAVANVMS
197 TVVAVANVM
195 PLTVVAVAN
180 LLVRGSADG
179 ALLVRGSAD
173 EARELVALL
155 FFTRQPRSR
151 MMRNFFTRQ
140 HWKVQRRAA
138 SEHWKVQRR
124 RVVSGGRSM
119 AFASFRVVS
112 SAFADRPAF
109 QQGSAFADR
95 VVLNGERAI
78 ARRYGDVFQ
77 LARRYGDVF
70 AHLSFARLA
65 AVGQAAHLS
63 AAAVGQAAH
62 NAAAVGQAA
57 WPLIGNAAA
40 LRQRRRQLR
25 LLLSVLATV
23 LLLLLSVLA
15 PLSIQQTTL
531 SAVQNLQAK
518 VNVTLRESM
513 PKSFKVNVT
506 SYGLTIKPK
504 NFSYGLTIK
502 KMNFSYGLT
496 NPNEPAKMN
485 SILAHQCDF
473 EELSKMQLF
470 CIGEELSKM
462 IFSVGKRRC
455 DLTSRVMIF
454 KDLTSRVMI
449 DGLINKDLT
444 RFLDKDGLI
441 DPARFLDKD

523 RESMELLDS
509 LTIKPKSFK
469 RCIGEELSK
445 FLDKDGLIN
433 KWPNPENFD
392 SSFVPVTIP
388 AMRFSSFVP
363 VVGRDRLPC
358 AELDQVVGR
282 SLRPGAAPR
247 LQYFPNPVR
241 VDVMPWLQY
234 TVGAGSLVD
186 ADGAFLDPR
165 VLEGHVLSE
160 PRSRQVLEG
120 FASFRVVSG
114 FADRPAFAS
63 AAAVGQAAH
43 RRRQLRSAP
41 RQRRRQLRS
33 VHVGQRLLR
511 IKPKSFKVN
494 RANPNEPAK
488 AHQCDFRAN
459 RVMIFSVGK
440 FDPARFLDK
431 PLKWPNPEN
416 KDTVVFVNQ
324 ITDIFGASQ
306 GDSHGGGAR
303 KAAGDSHGG
267 NFSNFILDK
251 PNPVRTVFR
231 FGRTVGAGS
230 EFGRTVGAG
215 SHDDPEFRE
179 ALLVRGSAD
176 ELVALLVRG
175 RELVALLVR
151 MMRNFFTRQ
130 RSMAFGHYS
102 AIHQALVQQ
101 RAIHQALVQ
96 VLNGERAIH
90 GSCPIVVLN
75 ARLARRYGD
60 IGNAAAVGQ
54 PFAWPLIGN
26 LLSVLATVH
7 PNDPWPLNP
4 SLSPNDPWP
3 TSLSPNDPW
532 AVQNLQAKE
529 LDSAVQNLQ
527 ELLDSAVQN
516 FKVNVTLRE
505 FSYGLTIKP
504 NFSYGLTIK

523 RESMELLDS
507 YGLTIKPKS
491 CDFRANPNE
466 GKRRCIGEE
419 VVFVNQWSV
397 VTIPHATTA
392 SSFVPVTIP
390 RFSSFVPVT
366 RDRLPCMGD
355 RVQAELDQV
329 GASQDTLST
325 TDIFGASQD
312 GARLDLENV
311 GGARLDLEN
278 RHCESLRPG
248 QYFPNPVRT
245 PWLQYFPNP
238 GSLVDVMPW
139 EHWKVQRRA
121 ASFRVVSGG
117 RPAFASFRV
90 GSCPIVVLN
83 DVFQIRLGS
82 GDVFQIRLG
55 FAWPLIGNA
53 GPFAWPLIG
52 PGPFAWPLI
48 RSAPPGPFA
21 TTLLLLLSV
534 QNLQAKETC
527 ELLDSAVQN
526 MELLDSAVQ
512 KPKSFKVNV
462 IFSVGKRRC
416 KDTVVFVNQ
411 GYHIPKDTV
409 VLGYHIPKD
373 GDQPNLPYV
359 ELDQVVGRD
326 DIFGASQDT
322 ATITDIFGA
302 KKAAGDSHG
286 GAAPRDMMD
255 RTVFREFEQ
229 EEFGRTVGA
184 GSADGAFLD
176 ELVALLVRG
164 QVLEGHVLS
156 FTRQPRSRQ
107 LVQQGSAFA
102 AIHQALVQQ
88 RLGSCPIVV
58 PLIGNAAAV
57 WPLIGNAAA
34 HVGQRLLRQ
25 LLLSVLATV
24 LLLLSVLAT
23 LLLLLSVLA
14 NPLSIQQTT

114 FADRPAFAS	427 VNHDPLKWP	495 ANPNEPAKM	13 LNPLSIQQT
103 IHQALVQQG	422 VNQWSVNHD	492 DFRANPNEP	2 GTSLSPNDP
101 RAIHQALVQ	390 RFSSFVPVT	486 ILAHQCDFR	516 FKVNVTLRE
91 SCPIVVLNG	388 AMRFSSFVP	481 FLFISILAH	511 IKPKSFKVN
84 VFQIRLGSC	384 FLYEAMRFS	464 SVGKRRCIG	510 TIKPKSFKV
77 LARRYGDVF	382 LAFLYEAMR	462 IFSVGKRRC	487 LAHQCDFRA
65 AVGQAAHLS	381 VLAFLYEAM	456 LTSRVMIFS	482 LFISILAHQ
50 APPGPFAWP	380 YVLAFLYEA	447 DKDGLINKD	480 LFLFISILA
11 WPLNPLSIQ	369 LPCMGDQPN	439 NFDPARFLD	452 INKDLTSRV
530 DSAVQNLQA	368 RLPCMGDQP	428 NHDPLKWPN	430 DPLKWPNPE
513 PKSFKVNVT	356 VQAELDQVV	427 VNHDPLKWP	429 HDPLKWPNP
464 SVGKRRCIG	348 RYPDVQTRV	415 PKDTVVFVN	380 YVLAFLYEA
456 LTSRVMIFS	345 LFTRYPDVQ	408 SVLGYHIPK	368 RLPCMGDQP
427 VNHDPLKWP	343 LLLFTRYPD	404 TANTSVLGY	357 QAELDQVVG
422 VNQWSVNHD	332 QDTLSTALQ	403 TTANTSVLG	350 PDVQTRVQA
410 LGYHIPKDT	325 TDIFGASQD	398 TIPHATTAN	333 DTLSTALQW
393 SFVPVTIPH	313 ARLDLENVP	393 SFVPVTIPH	315 LDLENVPAT
386 YEAMRFSSF	310 GGGARLDLE	379 PYVLAFLYE	308 SHGGGARLD
363 VVGRDRLPC	302 KKAAGDSHG	364 VGRDRLPCM	303 KAAGDSHGG
362 QVVGRDRLP	270 NFILDKFLR	359 ELDQVVGRD	299 SAEKKAAGD
333 DTLSTALQW	269 SNFILDKFL	357 QAELDQVVG	292 MMDAFILSA
308 SHGGGARLD	261 FEQLNRNFS	318 ENVPATITD	274 DKFLRHCES
295 AFILSAEKK	259 REFEQLNRN	313 ARLDLENVP	237 AGSLVDVMP
293 MDAFILSAE	254 VRTVFREFE	311 GGARLDLEN	235 VGAGSLVDV
279 HCESLRPGA	244 MPWLQYFPN	308 SHGGGARLD	234 TVGAGSLVD
278 RHCESLRPG	236 GAGSLVDVM	304 AAGDSHGGG	228 NEEFGRTVG
267 NFSNFILDK	235 VGAGSLVDV	302 KKAAGDSHG	196 LTVVAVANV
240 LVDVMPWLQ	232 GRTVGAGSL	301 EKKAAGDSH	191 LDPRPLTVV
184 GSADGAFLD	223 ELLSHNEEF	300 AEKKAAGDS	189 AFLDPRPLT
171 LSEARELVA	210 FGCRYSHDD	298 LSAEKKAAG	187 DGAFLDPRP
156 FTRQPRSRQ	201 VANVMSAVC	283 LRPGAAPRD	180 LLVRGSADG
147 AAHSMMRNF	199 VAVANVMSA	272 ILDKFLRHC	178 VALLVRGSA
146 RAAHSMMRN	191 LDPRPLTVV	271 FILDKFLRH	165 VLEGHVLSE
111 GSAFADRPA	172 SEARELVAL	236 GAGSLVDVM	125 VVSGGRSMA
83 DVFQIRLGS	166 LEGHVLSEA	228 NEEFGRTVG	118 PAFASFRVV
75 ARLARRYGD	163 RQVLEGHVL	224 LLSHNEEFG	105 QALVQQGSA
60 IGNAAAVGQ	162 SRQVLEGHV	220 EFRELLSHN	94 IVVLNGERA
35 VGQRLLRQR	159 QPRSRQVLE	208 VCFGCRYSH	92 CPIVVLNGE
6 SPNDPWPLN	158 RQPRSRQVL	204 VMSAVCFGC	91 SCPIVVLNG
2 GTSLSPNDP	148 AHSMMRNFF	203 NVMSAVCFG	67 GQAAHLSFA
523 RESMELLDS	139 EHWKVQRRA	198 VVAVANVMS	61 GNAAAVGQA
515 SFKVNVTLR	135 GHYSEHWKV	195 PLTVVAVAN	50 APPGPFAWP
506 SYGLTIKPK	133 AFGHYSEHW	161 RSRQVLEGH	12 PLNPLSIQQ
504 NFSYGLTIK	127 SGGRSMAFG	153 RNFFTRQPR	11 WPLNPLSIQ
475 LSKMQLFLF	123 FRVVSGGRS	145 RRAAHSMMR	1 MGTSLSPND
449 DGLINKDLT	120 FASFRVVSG	144 QRRAAHSMM	529 LDSAVQNLQ
432 LKWPNPENF	108 VQQGSAFAD	141 WKVQRRAAH	525 SMELLDSAV
405 ANTSVLGYH	107 LVQQGSAFA	136 HYSEHWKVQ	524 ESMELLDSA
357 QAELDQVVG	105 QALVQQGSA	133 AFGHYSEHW	517 KVNVTLRES
320 VPATITDIF	104 HQALVQQGS	129 GRSMAFGHY	513 PKSFKVNVT
310 GGGARLDLE	100 ERAIHQALV	127 SGGRSMAFG	484 ISILAHQCD
302 KKAAGDSHG	92 CPIVVLNGE	121 ASFRVVSGG	477 KMQLFLFIS
283 LRPGAAPRD	89 LGSCPIVVL	110 QGSAFADRP	471 IGEELSKMQ
280 CESLRPGAA	86 QIRLGSCPI	109 QQGSAFADR	457 TSRVMIFSV
255 RTVFREFEQ	85 FQIRLGSCP	108 VQQGSAFAD	433 KWPNPENFD
222 RELLSHNEE	79 RRYGDVFQI	103 IHQALVQQG	431 PLKWPNPEN
219 PEFRELLSH	75 ARLARRYGD	91 SCPIVVLNG	428 NHDPLKWPN
161 RSRQVLEGH	74 FARLARRYG	83 DVFQIRLGS	417 DTVVFVNQW
149 HSMMRNFFT	58 PLIGNAAAV	80 RYGDVFQIR	407 TSVLGYHIP

78 ARRYGDVFQ
74 FARLARRYG
73 SFARLARRY
54 PFAWPLIGN
52 PGPFAWPLI
534 QNLQAKETC
526 MELLDSAVQ
516 FKVNVTLRE
489 HQCDFRANP
484 ISILAHQCD
462 IFSVGKRRC
453 NKDLTSRVM
378 LPYVLAFLY
369 LPCMGDQPN
353 QTRVQAELD
349 YPDVQTRVQ
306 GDSHGGGAR
288 APRDMMDAF
285 PGAAPRDMM
284 RPGAAPRDM
257 VFREFEQLN
252 NPVRTVFRE
250 FPNPVRTVF
247 LQYFPNPVR
237 AGSLVDVMP
231 FGRTVGAGS
220 EFRELLSHN
215 SHDDPEFRE
202 ANVMSAVCF
160 PRSRQVLEG
144 QRRAAHSMM
140 HWKVQRRAA
127 SGGRSMAFG
126 VSGGRSMAF
108 VQQGSAFAD
97 LNGERAIHQ
85 FQIRLGSCP
82 GDVFQIRLG
66 VGQAAHLSF
33 VHVGQRLLR
9 DPWPLNPLS
529 LDSAVQNLQ
519 NVTLRESME
496 NPNEPAKMN
488 AHQCDFRAN
471 IGEELSKMQ
435 PNPENFDPA
434 WPNPENFDP
433 KWPNPENFD
428 NHDPLKWPN
418 TVVFVNQWS
407 TSVLGYHIP
385 LYEAMRFSS
383 AFLYEAMRF
367 DRLPCMGDQ
350 PDVQTRVQA
332 QDTLSTALQ
328 FGASQDTLS
325 TDIFGASQD

56 AWPLIGNAA
52 PGPFAWPLI
42 QRRRQLRSA
39 LLRQRRRQL
26 LLSVLATVH
22 TLLLLLSVL
535 NLQAKETCQ
527 ELLDSAVQN
526 MELLDSAVQ
519 NVTLRESME
508 GLTIKPKSF
501 AKMNFSYGL
491 CDFRANPNE
489 HQCDFRANP
483 FISILAHQC
479 QLFLFISIL
467 KRRCIGEEL
448 KDGLINKDL
443 ARFLDKDGL
438 ENFDPARFL
433 KWPNPENFD
421 FVNQWSVNH
419 VVFVNQWSV
414 IPKDTVVFV
413 HIPKDTVVF
411 GYHIPKDTV
401 HATTANTSV
396 PVTIPHATT
395 VPVTIPHAT
394 FVPVTIPHA
383 AFLYEAMRF
374 DQPNLPYVL
370 PCMGDQPNL
366 RDRLPCMGD
364 VGRDRLPCM
351 DVQTRVQAE
350 PDVQTRVQA
344 LLFTRYPDV
342 LLLLFTRYP
334 TLSTALQW
326 DIFGASQDT
320 VPATITDIF
317 LENVPATIT
315 LDLENVPAT
304 AAGDSHGGG
303 KAAGDSHGG
301 EKKAAGDSH
300 AEKKAAGDS
297 ILSAEKKAA
288 APRDMMDAF
287 AAPRDMMDA
283 LRPGAAPRD
273 LDKFLRHCE
265 NRNFSNFIL
262 EQLNRNFSN
252 NPVRTVFRE
246 WLQYFPNPV
243 VMPWLQYFP
230 EFGRTVGAG

74 FARLARRYG
65 AVGQAAHLS
59 LIGNAAAVG
46 QLRSAPPGP
45 RQLRSAPPG
44 RRQLRSAPP
36 GQRLLRQRR
34 HVGQRLLRQ
29 VLATVHVGQ
28 SVLATVHVG
535 NLQAKETCQ
526 MELLDSAVQ
522 LRESMELLD
515 SFKVNVTLR
506 SYGLTIKPK
498 NEPAKMNFS
490 QCDFRANPN
489 HQCDFRANP
483 FISILAHQC
466 GKRRCIGEE
458 SRVMIFSVG
453 NKDLTSRVM
451 LINKDLTSR
450 GLINKDLTS
442 PARFLDKDG
426 SVNHDPLKW
421 FVNQWSVNH
409 VLGYHIPKD
405 ANTSVLGYH
385 LYEAMRFSS
381 VLAFLYEAM
368 RLPCMGDQP
362 QVVGRDRLP
354 TRVQAELDQ
353 QTRVQAELD
351 DVQTRVQAE
347 TRYPDVQTR
343 LLLFTRYPD
341 WLLLLFTRY
333 DTLSTALQW
332 QDTLSTALQ
328 FGASQDTLS
323 TITDIFGAS
310 GGGARLDLE
299 SAEKKAAGD
295 AFILSAEKK
293 MDAFILSAE
291 DMMDAFILS
286 GAAPRDMMD
278 RHCESLRPG
277 LRHCESLRP
276 FLRHCESLR
266 RNFSNFILD
261 FEQLNRNFS
258 FREFEQLNR
257 VFREFEQLN
254 VRTVFREFE
245 PWLQYFPNP
238 GSLVDVMPW

401 HATTANTSV
399 IPHATTANT
394 FVPVTIPHA
388 AMRFSSFVP
362 QVVGRDRLP
356 VQAELDQVV
346 FTRYPDVQT
344 LLFTRYPDV
339 LQWLLLLFT
330 ASQDTLSTA
318 ENVPATITD
317 LENVPATIT
310 GGGARLDLE
300 AEKKAAGDS
298 LSAEKKAAG
296 FILSAEKKA
281 ESLRPGAAP
272 ILDKFLRHC
262 EQLNRNFSN
252 NPVRTVFRE
243 VMPWLQYFP
226 SHNEEFGRT
220 EFRELLSHN
211 GCRYSHDDP
199 VAVANVMSA
192 DPRPLTVVA
181 LVRGSADGA
179 ALLVRGSAD
166 LEGHVLSEA
151 MMRNFFTRQ
142 KVQRRAAHS
131 SMAFGHYSE
130 RSMAFGHYS
111 GSAFADRPA
108 VQQGSAFAD
104 HQALVQQGS
103 IHQALVQQG
98 NGERAIHQA
85 FQIRLGSCP
76 RLARRYGDV
70 AHLSFARLA
65 AVGQAAHLS
56 AWPLIGNAA
28 SVLATVHVG
20 QTTLLLLLS
9 DPWPLNPLS
7 PNDPWPLNP
3 TSLSPNDPW
535 NLQAKETCQ
533 VQNLQAKET
530 DSAVQNLQA
502 KMNFSYGLT
496 NPNEPAKMN
489 HQCDFRANP
483 FISILAHQC
449 DGLINKDLT
445 FLDKDGLIN
441 DPARFLDKD
434 WPNPENFDP

318 ENVPATITD	229 EEFGRTVGA	219 PEFRELLSH	426 SVNHDPLKW
281 ESLRPGAAP	224 LLSHNEEFG	211 GCRYSHDDP	422 VNQWSVNHD
277 LRHCESLRP	203 NVMSAVCFG	207 AVCFGCRYS	420 VFVNQWSVN
253 PVRTVFREF	202 ANVMSAVCF	205 MSAVCFGCR	418 TVVFVNQWS
241 VDVMPWLQY	193 PRPLTVVAV	201 VANVMSAVC	415 PKDTVVFVN
225 LSHNEEFGR	186 ADGAFLDPR	197 TVVAVANVM	414 IPKDTVVFV
214 YSHDDPEFR	183 RGSADGAFL	187 DGAFLDPRP	410 LGYHIPKDT
213 RYSHDDPEF	182 VRGSADGAF	177 LVALLVRGS	400 PHATTANTS
210 FGCRYSHDD	181 LVRGSADGA	167 EGHVLSEAR	396 PVTIPHATT
168 GHVLSEARE	177 LVALLVRGS	164 QVLEGHVLS	384 FLYEAMRFS
152 MRNFFTRQP	176 ELVALLVRG	150 SMMRNFFTR	379 PYVLAFLYE
148 AHSMMRNFF	153 RNFFTRQPR	146 RAAHSMMRN	375 QPNLPYVLA
141 WKVQRRAAH	147 AAHSMMRNF	143 VQRRAAHSM	369 LPCMGDQPN
137 YSEHWKVQR	145 RRAAHSMMR	142 KVQRRAAHS	343 LLLFTRYPD
133 AFGHYSEHW	144 QRRAAHSMM	137 YSEHWKVQR	342 LLLLFTRYP
130 RSMAFGHYS	143 VQRRAAHSM	132 MAFGHYSEH	332 QDTLSTALQ
122 SFRVVSGGR	141 WKVQRRAAH	128 GGRSMAFGH	328 FGASQDTLS
104 HQALVQQGS	136 HYSEHWKVQ	124 RVVSGGRSM	324 ITDIFGASQ
53 GPFAWPLIG	134 FGHYSEHWK	122 SFRVVSGGR	297 ILSAEKKAA
47 LRSAPPGPF	132 MAFGHYSEH	116 DRPAFASFR	293 MDAFILSAE
45 RQLRSAPPG	113 AFADRPAFA	72 LSFARLARR	249 YFPNPVRTV
3 TSLSPNDPW	103 IHQALVQQG	68 QAAHLSFAR	215 SHDDPEFRE
522 LRESMELLD	102 AIHQALVQQ	49 SAPPGPFAW	207 AVCFGCRYS
498 NEPAKMNFS	94 IVVLNGERA	38 RLLRQRRRQ	201 VANVMSAVC
492 DFRANPNEP	93 PIVVLNGER	20 QTTLLLLLS	200 AVANVMSAV
491 CDFRANPNE	87 IRLGSCPIV	2 GTSLSPNDP	195 PLTVVAVAN
468 RRCIGEELS	84 VFQIRLGSC	531 SAVQNLQAK	190 FLDPRPLTV
458 SRVMIFSVG	76 RLARRYGDV	518 VNVTLRESM	185 SADGAFLDP
440 FDPARFLDK	61 GNAAAVGQA	517 KVNVTLRES	177 LVALLVRGS
439 NFDPARFLD	59 LIGNAAAVG	507 YGLTIKPKS	159 QPRSRQVLE
436 NPENFDPAR	47 LRSAPPGPF	500 PAKMNFSYG	120 FASFRVVSG
430 DPLKWPNPE	46 QLRSAPPGP	491 CDFRANPNE	119 AFASFRVVS
429 HDPLKWPNP	43 RRRQLRSAP	484 ISILAHQCD	110 QGSAFADRP
423 NQWSVNHDP	36 GQRLLRQRR	482 LFISILAHQ	97 LNGERAIHQ
416 KDTVVFVNQ	35 VGQRLLRQR	477 KMQLFLFIS	60 IGNAAAVGQ
400 PHATTANTS	30 LATVHVGQR	471 IGEELSKMQ	59 LIGNAAAVG
372 MGDQPNLPY	11 WPLNPLSIQ	470 CIGEELSKM	54 PFAWPLIGN
366 RDRLPCMGD	8 NDPWPLNPL	468 RRCIGEELS	49 SAPPGPFAW
365 GRDRLPCMG		461 MIFSVGKRR	27 LSVLATVHV
360 LDQVVGRDR	HLA-A1 Decamers	460 VMIFSVGKR	4 SLSPNDPWP
345 LFTRYPDVQ		429 HDPLKWPNP	519 NVTLRESME
274 DKFLRHCES	Pos 1234567890	425 WSVNHDPLK	498 NEPAKMNFS
273 LDKFLRHCE	240 LVDVMPWLQY	422 VNQWSVNHD	492 DFRANPNEP
270 NFILDKFLR	403 TTANTSVLGY	420 VFVNQWSVN	490 QCDFRANPN
261 FEQLNRNFS	439 NFDPARFLDK	417 DTVVFVNQW	464 SVGKRRCIG
230 EFGRTVGAG	371 CMGDQPNLPY	400 PHATTANTS	456 LTSRVMIFS
221 FRELLSHNE	205 MSAVCFGCRY	384 FLYEAMRFS	442 PARFLDKDG
205 MSAVCFGCR	72 LSFARLARRY	382 LAFLYEAMR	427 VNHDPLKWP
187 DGAFLDPRP	377 NLPYVLAFLY	371 CMGDQPNLP	423 NQWSVNHDP
182 VRGSADGAF	340 QWLLLLFTRY	367 DRLPCMGDQ	403 TTANTSVLG
159 QPRSRQVLE	174 ARELVALLVR	365 GRDRLPCMG	398 TIPHATTAN
155 FFTRQPRSR	128 GGRSMAFGHY	360 LDQVVGRDR	395 VPVTIPHAT
154 NFFTRQPRS	216 HDDPEFRELL	345 LFTRYPDVQ	387 EAMRFSSFV
145 RRAAHSMMR	190 FLDPRPLTVV	342 LLLLFTRYP	321 PATITDIFG
139 EHWKVQRRA	137 YSEHWKVQRR	321 PATITDIFG	304 AAGDSHGGG
128 GGRSMAFGH	522 LRESMELLDS	294 DAFILSAEK	287 AAPRDMMDA

109 QQGSAFADR
44 RRQLRSAPP
43 RRRQLRSAP
40 LRQRRRQLR
37 QRLLRQRRR
36 GQRLLRQRR
511 IKPKSFKVN
499 EPAKMNFSY
465 VGKRRCIGE
425 WSVNHDPLK
420 VFVNQWSVN
415 PKDTVVFVN
354 TRVQAELDQ
300 AEKKAAGDS
266 RNFSNFILD
262 EQLNRNFSN
254 VRTVFREFE
251 PNPVRTVFR
245 PWLQYFPNP
244 MPWLQYFPN
212 CRYSHDDPE
136 HYSEHWKVQ
134 FGHYSEHWK
129 GRSMAFGHY
123 FRVVSGGRS
110 QGSAFADRP
80 RYGDVFQIR

41 RQRRRQLRS

1 MGTSLSPND
437 PENFDPARF
167 EGHVLSEAR
497 PNEPAKMNF

379 PYVLAFLYE
301 EKKAAGDSH
218 DPEFRELLS
260 EFEQLNRNF

HLA-A*0201 Decamers

Pos 1234567890
24 LLLLSVLATV
190 FLDPRPLTVV
88 RLGSCPIVVL
17 SIQQTTLLLL
527 ELLDSAVQNL
413 HIPKDTVVFV
343 LLLFTRYPDV
26 LLSVLATVHV
23 LLLLLSVLAT
4 SLSPNDPWPL
336 STALQWLLLL
456 LTSRVMIFSV
326 DIFGASQDTL
195 PLTVVAVANV

498 NEPAKMNFSY
445 FLDKDGLINK
336 STALQWLLLL
324 ITDIFGASQD
218 DPEFRELLSH
215 SHDDPEFREL
90 GSCPIVVLNG
497 PNEPAKMNFS
428 NHDPLKWPNP
331 SQDTLSTALQ
233 RTVGAGSLVD
171 LSEARELVAL
114 FADRPAFASF
81 YGDVFQIRLG
7 PNDPWPLNPL
528 LLDSAVQNLQ
525 SMELLDSAVQ
475 LSKMQLFLFI
415 PKDTVVFVNQ
385 LYEAMRFSSF
349 YPDVQTRVQA
185 SADGAFLDPR
184 GSADGAFLDP
165 VLEGHVLSEA
472 GEELSKMQLF
453 NKDLTSRVMI
447 DKDGLINKDL

425 WSVNHDPLKW

359 ELDQVVGRDR
353 QTRVQAELDQ
335 LSTALQWLLL
314 RLDLENVPAT

305 AGDSHGGGAR
299 SAEKKAAGDS
272 ILDKFLRHCE
227 HNEEFGRTVG
20 QTTLLLLLSV

16 LSIQQTTLLL

490 QCDFRANPNE
397 VTIPHATTAN
357 QAELDQVVGR
316 DLENVPATIT
260 EFEQLNRNFS
258 FREFEQLNRN
221 FRELLSHNEE
471 IGEELSKMQL
436 NPENFDPARF
392 SSFVPVTIPH
372 MGDQPNLPYV
365 GRDRLPCMGD
322 ATITDIFGAS
308 SHGGGARLDL
292 MMDAFILSAE
289 PRDMMDAFIL

273 LDKFLRHCE
262 EQLNRNFSN
259 REFEQLNRN
255 RTVFREFEQ
243 VMPWLQYFP
240 LVDVMPWLQ
222 RELLSHNEE
214 YSHDDPEFR
212 CRYSHDDPE
209 CFGCRYSHD
206 SAVCFGCRY
184 GSADGAFLD
180 LLVRGSADG
168 GHVLSEARE
154 NFFTRQPRS
152 MRNFFTRQP
138 SEHWKVQRR
131 SMAFGHYSE
123 FRVVSGGRS
104 HQALVQQGS
97 LNGERAIHQ
85 FQIRLGSCP
73 SFARLARRY
40 LRQRRRQLR
30 LATVHVGQR
12 PLNPLSIQQ
1 MGTSLSPND

HLA-B*0702 Decamers

Pos 1234567890
50 APPGPFAWPL

192 DPRPLTVVAV
288 APRDMMDAFI
369 LPCMGDQPNL
14 NPLSIQQTTL
375 QPNLPYVLAF

349 YPDVQTRVQA

284 RPGAAPRDMM
117 RPAFASFRVV
512 KPKSFKVNVT
434 WPNPENFDPA
51 PPGPFAWPLI
9 DPWPLNPLSI
57 WPLIGNAAAV
436 NPENFDPARF
395 VPVTIPHATT
252 NPVRTVFREF
496 NPNEPAKMNF
308 SHGGGARLDL
250 FPNPVRTVFR
159 QPRSRQVLEG
88 RLGSCPIVVL
513 PKSFKVNVTL

279 HCESLRPGA
261 FEQLNRNFS
231 FGRTVGAGS
227 HNEEFGRTV
198 VVAVANVMS
171 LSEARELVA
136 HYSEHWKVQ
133 AFGHYSEHW
127 SGGRSMAFG
114 FADRPAFAS
113 AFADRPAFA
84 VFQIRLGSC
29 VLATVHVGQ
6 SPNDPWPLN
500 PAKMNFSYG
488 AHQCDFRAN
465 VGKRRCIGE
439 NFDPARFLD
435 PNPENFDPA
385 LYEAMRFSS
371 CMGDQPNLP
363 VVGRDRLPC
353 QTRVQAELD
351 DVQTRVQAE
349 YPDVQTRVQ
345 LFTRYPDVQ
323 TITDIFGAS

305 AGDSHGGGA

291 DMMDAFILS
280 CESLRPGAA
273 LDKFLRHCE
257 VFREFEQLN

246 WLQYFPNPV
244 MPWLQYFPN
240 LVDVMPWLQ
230 EFGRTVGAG
218 DPEFRELLS

210 FGCRYSHDD

209 CFGCRYSHD
204 VMSAVCFGC
203 NVMSAVCFG
170 VLSEARELV
149 HSMMRNFFT
74 FARLARRYG
62 NAAAVGQAA
46 QLRSAPPGP

HLA-B8 Octamers

Pos 12345678
159 QPRSRQVL
521 TLRESMEL
510 TIKPKSFK
218 DPEFRELL

165 VLEGHVLSEA	279 HCESLRPGAA	499 EPAKMNFSYG	173 EARELVAL
38 RLLRQRRRQL	228 NEEFGRTVGA	473 EELSKMQLFL	515 SFKVNVTL
451 LINKDLTSRV	98 NGERAIHQAL	388 AMRFSSFVPV	414 IPKDTVVF
388 AMRFSSFVPV	17 SIQQTTLLLL	330 ASQDTLSTAL	276 FLRHCESL
338 ALQWLLLLFT	9 DPWPLNPLSI	194 RPLTVVAVAN	473 EELSKMQL
509 LTIKPKSFKV	521 TLRESMELLD	171 LSEARELVAL	475 LSKMQLFL
502 KMNFSYGLTI	520 VTLRESMELL	63 AAAVGQAAHL	455 DLTSRVMI
334 TLSTALQWLL	402 ATTANTSVLG	15 PLSIQQTTLL	444 RFLDKDGL
314 RLDLENVPAT	378 LPYVLAFLYE	4 SLSPNDPWPL	39 LLRQRRRQ
291 DMMDAFILSA	290 RDMMDAFILS	447 DKDGLINKDL	465 VGKRRCIG
263 QLNRNFSNFI	270 NFILDKFLRH	414 IPKDTVVFVN	310 GGGARLDL
234 TVGAGSLVDV	265 NRNFSNFILD	378 LPYVLAFLYE	257 VFREFEQL
172 SEARELVALL	255 RTVFREFEQL	376 PNLPYVLAFL	170 VLSEAREL
63 AAAVGQAAHL	170 VLSEARELVA	336 STALQWLLLL	362 QVVGRDRL
21 TTLLLLLSVL	49 SAPPGPFAWP	335 LSTALQWLLL	40 LRQRRRQL
20 QTTLLLLLSV	32 TVHVGQRLLR	306 GDSHGGGARL	6 SPNDPWPL
477 KMQLFLFISI	31 ATVHVGQRLL	216 HDDPEFRELL	508 GLTIKPKS
450 GLINKDLTSR	515 SFKVNVTLRE	182 VRGSADGAFL	450 GLINKDLT
333 DTLSTALQWL	510 TIKPKSFKVN	172 SEARELVALL	378 LPYVLAFL
248 QYFPNPVRTV	509 LTIKPKSFKV	157 TRQPRSRQVL	375 QPNLPYVL
86 QIRLGSCPIV	457 TSRVMIFSVG	68 QAAHLSFARL	353 QTRVQAEL
486 ILAHQCDFRA	407 TSVLGYHIPK	18 IQQTTLLLLL	23 LLLLLSVL
481 FLFISILAHQ	362 QVVGRDRLPC	16 LSIQQTTLLL	535 NLQAKETC
315 LDLENVPATI	346 FTRYPDVQTR	7 PNDPWPLNPL	512 KPKSFKVN
192 DPRPLTVVAV	338 ALQWLLLLFT	527 ELLDSAVQNL	498 NEPAKMNF
189 AFLDPRPLTV	337 TALQWLLLLF	466 GKRRCIGEEL	464 SVGKRRCI
171 LSEARELVAL	276 FLRHCESLRP	442 PARFLDKDGL	431 PLKWPNPE
170 VLSEARELVA	217 DDPEFRELLS	430 DPLKWPNPEN	338 ALQWLLLL
106 ALVQQGSAFA	173 EARELVALLV	401 HATTANTSVL	299 SAEKKAAG
68 QAAHLSFARL	70 AHLSFARLAR	399 IPHATTANTS	17 SIQQTTLL
22 TLLLLLSVLA	48 RSAPPGPFAW	373 GDQPNLPYVL	9 DPWPLNPL
12 PLNPLSIQQT	33 VHVGQRLLRQ	334 TLSTALQWLL	384 FLYEAMRF
520 VTLRESMELL	23 LLLLLSVLAT	326 DIFGASQDTL	364 VGRDRLPC
408 SVLGYHIPKD	19 QQTTLLLLLS	320 VPATITDIFG	271 FILDKFLR
376 PNLPYVLAFL	18 IQQTTLLLLL	264 LNRNFSNFIL	251 PNPVRTVF
351 DVQTRVQAEL	6 SPNDPWPLNP	255 RTVFREFEQL	190 FLDPRPLT
311 GGARLDLENV	529 LDSAVQNLQA	244 MPWLQYFPNP	179 ALLVRGSA
226 SHNEEFGRTV	514 KSFKVNVTLR	231 FGRTVGAGSL	149 HSMMRNFF
198 VVAVANVMSA	502 KMNFSYGLTI	218 DPEFRELLSH	500 PAKMNFSY
180 LLVRGSADGA	479 QLFLFISILA	215 SHDDPEFREL	474 ELSKMQLF
29 VLATVHVGQR	477 KMQLFLFISI	187 DGAFLDPRPL	344 LLFTRYPD
18 IQQTTLLLLL	463 FSVGKRRCIG	80 RYGDVFQIRL	337 TALQWLLL
15 PLSIQQTTLL	444 RFLDKDGLIN	38 RLLRQRRRQL	282 SLRPGAAP
384 FLYEAMRFSS	434 WPNPENFDPA	31 ATVHVGQRLL	113 AFADRPAF
271 FILDKFLRHC	417 DTVVFVNQWS	17 SIQQTTLLLL	76 RLARRYGD
199 VAVANVMSAV	412 YHIPKDTVVF	6 SPNDPWPLNP	41 RQRRRQLR
179 ALLVRGSADG	375 QPNLPYVLAF	529 LDSAVQNLQA	486 ILAHQCDF
169 HVLSEARELV	328 FGASQDTLST	471 IGEELSKMQL	479 QLFLFISI
87 IRLGSCPIVV	307 DSHGGGARLD	441 DPARFLDKDG	445 FLDKDGLI
31 ATVHVGQRLL	282 SLRPGAAPRD	437 PENFDPARFL	377 NLPYVLAF

519 NVTLRESMEL
494 RANPNEPAKM

479 QLFLFISILA
478 MQLFLFISIL
445 FLDKDGLINK
418 TVVFVNQWSV
410 LGYHIPKDTV
372 MGDQPNLPYV
342 LLLLFTRYPD
329 GASQDTLSTA
308 SHGGGARLDL

297 ILSAEKKAAG

296 FILSAEKKAA

282 SLRPGAAPRD
215 SHDDPEFREL
164 QVLEGHVLSE
156 FTRQPRSRQV
94 IVVLNGERAI

71 HLSFARLARR
57 WPLIGNAAAV
30 LATVHVGQRL

16 LSIQQTTLLL
511 IKPKSFKVNV
469 RCIGEELSKM
398 TIPHATTANT
386 YEAMRFSSFV
381 VLAFLYEAMR
373 GDQPNLPYVL
363 VVGRDRLPCM
355 RVQAELDQVV
354 TRVQAELDQV
330 ASQDTLSTAL
238 GSLVDVMPWL
177 LVALLVRGSA

173 EARELVALLV
102 AIHQALVQQG
96 VLNGERAIHQ
75 ARLARRYGDV
55 FAWPLIGNAA

50 APPGPFAWPL
25 LLLSVLATVH
14 NPLSIQQTTL
7 PNDPWPLNPL
528 LLDSAVQNLQ
521 TLRESMELLD

471 IGEELSKMQL
466 GKRRCIGEEL

409 VLGYHIPKDT

257 VFREFEQLNR
225 LSHNEEFGRT

196 LTVVAVANVM
189 AFLDPRPLTV
164 QVLEGHVLSE
159 QPRSRQVLEG
156 FTRQPRSRQV
149 HSMMRNFFTR
100 ERAIHQALVQ
96 VLNGERAIHQ
82 GDVFQIRLGS

65 AVGQAAHLSF

21 TTLLLLLSVL

4 SLSPNDPWPL
2 GTSLSPNDPW
505 FSYGLTIKPK
504 NFSYGLTIKP
494 RANPNEPAKM

480 LFLFISILAH
473 EELSKMQLFL
468 RRCIGEELSK

464 SVGKRRCIGE
456 LTSRVMIFSV
449 DGLINKDLTS
406 NTSVLGYHIP
393 SFVPVTIPHA
391 FSSFVPVTIP
333 DTLSTALQWL
332 QDTLSTALQW
310 GGGARLDLEN
291 DMMDAFILSA
266 RNFSNFILDK
214 YSHDDPEFRE
157 TRQPRSRQVL

126 VSGGRSMAFG
87 IRLGSCPIVV
55 FAWPLIGNAA
52 PGPFAWPLIG
51 PPGPFAWPLI

40 LRQRRRQLRS
27 LSVLATVHVG
5 LSPNDPWPLN
455 DLTSRVMIFS
408 SVLGYHIPKD
373 GDQPNLPYVL

367 DRLPCMGDQP
330 ASQDTLSTAL

320 VPATITDIFG

423 NQWSVNHDPL
413 HIPKDTVVFV

412 YHIPKDTVVF
390 RFSSFVPVTI
360 LDQVVGRDRL
351 DVQTRVQAEL
338 ALQWLLLLFT
314 RLDLENVPAT
313 ARLDLENVPA
289 PRDMMDAFIL
268 FSNFILDKFL

238 GSLVDVMPWL

235 VGAGSLVDVM

181 LVRGSADGAF
173 EARELVALLV
170 VLSEARELVA
162 SRQVLEGHVL
148 AHSMMRNFFT

125 VVSGGRSMAF
98 NGERAIHQAL
78 ARRYGDVFQI

65 AVGQAAHLSF
53 GPFAWPLIGN
47 LRSAPPGPFA
26 LLSVLATVHV
21 TTLLLLLSVL
520 VTLRESMELL
519 NVTLRESMEL
511 IKPKSFKVNV
500 PAKMNFSYGL
492 DFRANPNEPA
478 MQLFLFISIL
475 LSKMQLFLFI
474 ELSKMQLFLF

462 IFSVGKRRCI
453 NKDLTSRVMI
333 DTLSTALQWL
328 FGASQDTLST
274 DKFLRHCESL

234 TVGAGSLVDV
191 LDPRPLTVVA
190 FLDPRPLTVV
189 AFLDPRPLTV
168 GHVLSEAREL
147 AAHSMMRNFF

139 EHWKVQRRAA
111 GSAFADRPAF

110 QGSAFADRPA

336 STALQWLL
320 VPATITDI

286 GAAPRDMM
120 FASFRVVS
96 VLNGERAI
78 ARRYGDVF
53 GPFAWPLI
429 HDPLKWPN
387 EAMRFSSF
312 GARLDLEN
308 SHGGGARL

301 EKKAAGDS

298 LSAEKKAA

288 APRDMMDA
264 LNRNFSNF
224 LLSHNEEF
217 DDPEFREL
192 DPRPLTVV

164 QVLEGHVL
140 HWKVQRRA
138 SEHWKVQR

100 ERAIHQAL
74 FARLARRY
46 QLRSAPPG
11 WPLNPLSI
463 FSVGKRRC
452 INKDLTSR
332 QDTLSTAL
328 FGASQDTL
270 NFILDKFL
240 LVDVMPWL
184 GSADGAFL
174 ARELVALL
90 GSCPIVVL

86 QIRLGSCP
82 GDVFQIRL
33 VHVGQRLL
32 TVHVGQRL
20 QTTLLLLL

18 IQQTTLLL
529 LDSAVQNL
522 LRESMELL
513 PKSFKVNV
502 KMNFSYGL
480 LFLFISIL

468 RRCIGEEL
449 DGLINKDL

446 LDKDGLIN

401 HATTANTSVL	268 FSNFILDKFL	106 ALVQQGSAFA	442 PARFLDKD
393 SFVPVTIPHA	250 FPNPVRTVFR	99 GERAIHQALV	439 NFDPARFL
380 YVLAFLYEAM	248 QYFPNPVRTV	92 CPIVVLNGER	425 WSVNHDPL
369 LPCMGDQPNL	239 SLVDVMPWLQ	87 IRLGSCPIVV	412 YHIPKDTV
347 TRYPDVQTRV	192 DPRPLTVVAV	56 AWPLIGNAAA	403 TTANTSVL
344 LLFTRYPDVQ	172 SEARELVALL	30 LATVHVGQRL	371 CMGDQPNL
306 GDSHGGGARL	150 SMMRNFFTRQ	23 LLLLLSVLAT	335 LSTALQWL
292 MMDAFILSAE	121 ASFRVVSGGR	11 WPLNPLSIQQ	321 PATITDIF
288 APRDMMDAFI	115 ADRPAFASFR	524 ESMELLDSAV	300 AEKKAAGD
286 GAAPRDMMDA	111 GSAFADRPAF	523 RESMELLDSA	291 DMMDAFIL
272 ILDKFLRHCE	108 VQQGSAFADR	502 KMNFSYGLTI	273 LDKFLRHC
255 RTVFREFEQL	12 PLNPLSIQQT	501 AKMNFSYGLT	266 RNFSNFIL
239 SLVDVMPWLQ	531 SAVQNLQAKE	494 RANPNEPAKM	262 EQLNRNFS
235 VGAGSLVDVM	530 DSAVQNLQAK	469 RCIGEELSKM	233 RTVGAGSL
231 FGRTVGAGSL	524 ESMELLDSAV	389 MRFSSFVPVT	229 EEFGRTVG
224 LLSHNEEFGR	506 SYGLTIKPKS	355 RVQAELDQVV	220 EFRELLSH
182 VRGSADGAFL	484 ISILAHQCDF	318 ENVPATITDI	189 AFLDPRPL
168 GHVLSEAREL	432 LKWPNPENFD	304 AAGDSHGGGA	97 LNGERAIH
162 SRQVLEGHVL	388 AMRFSSFVPV	291 DMMDAFILSA	77 LARRYGDV
131 SMAFGHYSEH	376 PNLPYVLAFL	287 AAPRDMMDAF	70 AHLSFARL
112 SAFADRPAFA	347 TRYPDVQTRV	278 RHCESLRPGA	65 AVGQAAHL
99 GERAIHQALV	318 ENVPATITDI	249 YFPNPVRTVF	52 PGPFAWPL
97 LNGERAIHQA	317 LENVPATITD	228 NEEFGRTVGA	19 QQTTLLLL
78 ARRYGDVFQI	298 LSAEKKAAGD	193 PRPLTVVAVA	16 LSIQQTTL
59 LIGNAAAVGQ	286 GAAPRDMMDA	161 RSRQVLEGHV	519 NVTLRESM
58 PLIGNAAAVG	281 ESLRPGAAPR	114 FADRPAFASF	440 FDPARFLD
9 DPWPLNPLSI	269 SNFILDKFLR	112 SAFADRPAFA	392 SSFVPVTI
517 KVNVTLRESM	249 YFPNPVRTVF	86 QIRLGSCPIV	280 CESLRPGA
500 PAKMNFSYGL	242 DVMPWLQYFP	76 RLARRYGDVF	274 DKFLRHCE
485 SILAHQCDFR	238 GSLVDVMPWL	75 ARLARRYGDV	126 VSGGRSMA
403 TTANTSVLGY	235 VGAGSLVDVM	61 GNAAAVGQAA	122 SFRVVSGG
390 RFSSFVPVTI	204 VMSAVCFGCR	60 IGNAAAVGQA	84 VFQIRLGS
360 LDQVVGRDRL	162 SRQVLEGHVL	46 QLRSAPPGPF	44 RRQLRSAP
341 WLLLLFTRYP	161 RSRQVLEGHV	41 RQRRRQLRSA	37 QRLLRQRR
335 LSTALQWLLL	130 RSMAFGHYSE	532 AVQNLQAKET	34 HVGQRLLR
323 TITDIFGASQ	117 RPAFASFRVV	517 KVNVTLRESM	527 ELLDSAVQ
316 DLENVPATIT	80 RYGDVFQIRL	486 ILAHQCDFRA	499 EPAKMNFS
304 AAGDSHGGGA	79 RRYGDVFQIR	477 KMQLFLFISI	496 NPNEPAKM
276 FLRHCESLRP	64 AAVGQAAHLS	456 LTSRVMIFSV	490 QCDFRANP
274 DKFLRHCESL	53 GPFAWPLIGN	454 KDLTSRVMIF	476 SKMQLFLF
264 LNRNFSNFIL	39 LLRQRRRQLR	452 INKDLTSRVM	438 ENFDPARF
216 HDDPEFRELL	11 WPLNPLSIQQ	451 LINKDLTSRV	409 VLGYHIPK
185 SADGAFLDPR	3 TSLSPNDPWP	448 KDGLINKDLT	386 YEAMRFSS
176 ELVALLVRGS	501 AKMNFSYGLT	443 ARFLDKDGLI	359 ELDQVVGR
157 TRQPRSRQVL	499 EPAKMNFSYG	411 GYHIPKDTVV	351 DVQTRVQA
142 KVQRRAAHSM	487 LAHQCDFRAN	405 ANTSVLGYHI	346 FTRYPDVQ
134 FGHYSEHWKV	474 ELSKMQLFLF	400 PHATTANTSV	269 SNFILDKF
119 AFASFRVVSG	469 RCIGEELSKM	398 TIPHATTANT	261 FEQLNRNF

101 RAIHQALVQQ	459 RVMIFSVGKR	393 SFVPVTIPHA	255 RTVFREFE
76 RLARRYGDVF	443 ARFLDKDGLI	386 YEAMRFSSFV	254 VRTVFREF
39 LLRQRRRQLR	440 FDPARFLDKD	385 LYEAMRFSSF	239 SLVDVMPW
532 AVQNLQAKET	438 ENFDPARFLD	380 YVLAFLYEAM	223 ELLSHNEE
525 SMELLDSAVQ	384 FLYEAMRFSS	374 DQPNLPYVLA	211 GCRYSHDD
524 ESMELLDSAV	381 VLAFLYEAMR	372 MGDQPNLPYV	209 CFGCRYSH
474 ELSKMQLFLF	370 PCMGDQPNLP	363 VVGRDRLPCM	176 ELVALLVR
459 RVMIFSVGKR	352 VQTRVQAELD	347 TRYPDVQTRV	171 LSEARELV
443 ARFLDKDGLI	334 TLSTALQWLL	345 LFTRYPDVQT	157 TRQPRSRQ
442 PARFLDKDGL	309 HGGGARLDLE	337 TALQWLLLLF	154 NFFTRQPR
423 NQWSVNHDPL	295 AFILSAEKKA	329 GASQDTLSTA	142 KVQRRAAH
421 FVNQWSVNHD	262 EQLNRNFSNF	319 NVPATITDIF	141 WKVQRRAA
411 GYHIPKDTVV	252 NPVRTVFREF	295 AFILSAEKKA	127 SGGRSMAF
400 PHATTANTSV	246 WLQYFPNPVR	286 GAAPRDMMDA	75 ARLARRYG
394 FVPVTIPHAT	244 MPWLQYFPNP	283 LRPGAAPRDM	72 LSFARLAR
337 TALQWLLLLF	232 GRTVGAGSLV	267 NFSNFILDKF	36 GQRLLRQR
318 ENVPATITDI	226 SHNEEFGRTV	262 EQLNRNFSNF	4 SLSPNDPW
313 ARLDLENVPA	188 GAFLDPRPLT	248 QYFPNPVRTV	504 NFSYGLTI
196 LTVVAVANVM	169 HVLSEARELV	247 LQYFPNPVRT	481 FLFISILA
188 GAFLDPRPLT	134 FGHYSEHWKV	201 VANVMSAVCF	477 KMQLFLFI
150 SMMRNFFTRQ	122 SFRVVSGGRS	199 VAVANVMSAV	466 GKRRCIGE
117 RPAFASFRVV	89 LGSCPIVVLN	198 VVAVANVMSA	457 TSRVMIFS
85 FQIRLGSCPI	76 RLARRYGDVF	195 PLTVVAVANV	407 TSVLGYHI
80 RYGDVFQIRL	73 SFARLARRYG	188 GAFLDPRPLT	399 IPHATTAN
60 IGNAAAVGQA	69 AAHLSFARLA	177 LVALLVRGSA	395 VPVTIPHA
28 SVLATVHVGQ	68 QAAHLSFARL	165 VLEGHVLSEA	381 VLAFLYEA
531 SAVQNLQAKE	58 PLIGNAAAVG	156 FTRQPRSRQV	366 RDRLPCMG
523 RESMELLDSA	29 VLATVHVGQR	146 RAAHSMMRNF	349 YPDVQTRV
513 PKSFKVNVTL	22 TLLLLLSVLA	143 VQRRAAHSMM	342 LLLLFTRY
508 GLTIKPKSFK	15 PLSIQQTTLL	124 RVVSGGRSMA	341 WLLLLFTR
475 LSKMQLFLFI	8 NDPWPLNPLS	94 IVVLNGERAI	339 LQWLLLLF
473 EELSKMQLFL	527 ELLDSAVQNL	69 AAHLSFARLA	317 LENVPATI
462 IFSVGKRRCI	518 VNVTLRESME	66 VGQAAHLSFA	314 RLDLENVP
453 NKDLTSRVMI	512 KPKSFKVNVT	55 FAWPLIGNAA	297 ILSAEKKA
447 DKDGLINKDL	507 YGLTIKPKSF	22 TLLLLLSVLA	272 ILDKFLRH
426 SVNHDPLKWP	495 ANPNEPAKMN	20 QTTLLLLLSV	250 FPNPVRTV
405 ANTSVLGYHI	488 AHQCDFRANP	509 LTIKPKSFKV	246 WLQYFPNP
397 VTIPHATTAN	485 SILAHQCDFR	484 ISILAHQCDF	244 MPWLQYFP
389 MRFSSFVPVT	481 FLFISILAHQ	409 VLGYHIPKDT	243 VMPWLQYF
371 CMGDQPNLPY	476 SKMQLFLFIS	396 PVTIPHATTA	231 FGRTVGAG
368 RLPCMGDQPN	467 KRRCIGEELS	394 FVPVTIPHAT	195 PLTVVAVA
357 QAELDQVVGR	460 VMIFSVGKRR	343 LLLFTRYPDV	165 VLEGHVLS
346 FTRYPDVQTR	458 SRVMIFSVGK	316 DLENVPATIT	156 FTRQPRSR
328 FGASQDTLST	448 KDGLINKDLT	315 LDLENVPATI	143 VQRRAAHS
303 KAAGDSHGGG	446 LDKDGLINKD	311 GGARLDLENV	128 GGRSMAFG
268 FSNFILDKFL	426 SVNHDPLKWP	296 FILSAEKKAA	99 GERAIHQA
246 WLQYFPNPVR	424 QWSVNHDPLK	279 HCESLRPGAA	92 CPIVVLNG
245 PWLQYFPNPV	422 VNQWSVNHDP	263 QLNRNFSNFI	87 IRLGSCPI

232 GRTVGAGSLV	421 FVNQWSVNHD	259 REFEQLNRNF	71 HLSFARLA
200 AVANVMSAVC	419 VVFVNQWSVN	245 PWLQYFPNPV	67 GQAAHLSF
187 DGAFLDPRPL	414 IPKDTVVFVN	225 LSHNEEFGRT	29 VLATVHVG
161 RSRQVLEGHV	409 VLGYHIPKDT	222 RELLSHNEEF	26 LLSVLATV
98 NGERAIHQAL	405 ANTSVLGYHI	212 CRYSHDDPEF	24 LLLLSVLA
83 DVFQIRLGSC	389 MRFSSFVPVT	196 LTVVAVANVM	22 TLLLLLSV
69 AAHLSFARLA	386 YEAMRFSSFV	169 HVLSEARELV	531 SAVQNLQA
49 SAPPGPFAWP	380 YVLAFLYEAM	142 KVQRRAAHSM	528 LLDSAVQN
46 QLRSAPPGPF	374 DQPNLPYVLA	116 DRPAFASFRV	509 LTIKPKSF
41 RQRRRQLRSA	364 VGRDRLPCMG	105 QALVQQGSAF	492 DFRANPNE
512 KPKSFKVNVT	361 DQVVGRDRLP	104 HQALVQQGSA	485 SILAHQCD
483 FISILAHQCD	358 AELDQVVGRD	97 LNGERAIHQA	470 CIGEELSK
480 LFLFISILAH	356 VQAELDQVVG	85 FQIRLGSCPI	467 KRRCIGEE
470 CIGEELSKMQ	344 LLFTRYPDVQ	54 PFAWPLIGNA	456 LTSRVMIF
461 MIFSVGKRRC	342 LLLLFTRYPD	24 LLLLSVLATV	441 DPARFLDK
460 VMIFSVGKRR	327 IFGASQDTLS	12 PLNPLSIQQT	436 NPENFDPA
446 LDKDGLINKD	313 ARLDLENVPA	507 YGLTIKPKSF	434 WPNPENFD
404 TANTSVLGYH	304 AAGDSHGGGA	479 QLFLFISILA	433 KWPNPENF
395 VPVTIPHATT	300 AEKKAAGDSH	472 GEELSKMQLF	430 DPLKWPNP
377 NLPYVLAFLY	294 DAFILSAEKK	431 PLKWPNPENF	388 AMRFSSFV
358 AELDQVVGRD	284 RPGAAPRDMM	418 TVVFVNQWSV	369 LPCMGDQP
339 LQWLLLLFTR	275 KFLRHCESLR	410 LGYHIPKDTV	368 RLPCMGDQ
322 ATITDIFGAS	267 NFSNFILDKF	382 LAFLYEAMRF	343 LLLFTRYP
321 PATITDIFGA	261 FEQLNRNFSN	379 PYVLAFLYEA	334 TLSTALQW
298 LSAEKKAAGD	256 TVFREFEQLN	362 QVVGRDRLPC	316 DLENVPAT
295 AFILSAEKKA	237 AGSLVDVMPW	354 TRVQAELDQV	290 RDMMDAFI
243 VMPWLQYFPN	229 EEFGRTVGAG	325 TDIFGASQDT	289 PRDMMDAF
223 ELLSHNEEFG	208 VCFGCRYSHD	321 PATITDIFGA	284 RPGAAPRD
204 VMSAVCFGCR	207 AVCFGCRYSH	297 ILSAEKKAAG	265 NRNFSNFI
181 LVRGSADGAF	206 SAVCFGCRYS	241 VDVMPWLQYF	263 QLNRNFSN
120 FASFRVVSGG	202 ANVMSAVCFG	237 AGSLVDVMPW	253 PVRTVFRE
116 DRPAFASFRV	200 AVANVMSAVC	233 RTVGAGSLVD	252 NPVRTVFR
114 FADRPAFASF	198 VVAVANVMSA	232 GRTVGAGSLV	214 YSHDDPEF
95 VVLNGERAIH	197 TVVAVANVMS	226 SHNEEFGRTV	206 SAVCFGCR
93 PIVVLNGERA	195 PLTVVAVANV	180 LLVRGSADGA	203 NVMSAVCF
66 VGQAAHLSFA	193 PRPLTVVAVA	138 SEHWKVQRRA	201 VANVMSAV
65 AVGQAAHLSF	183 RGSADGAFLD	134 FGHYSEHWKV	194 RPLTVVAV
64 AAVGQAAHLS	182 VRGSADGAFL	123 FRVVSGGRSM	188 GAFLDPRP
62 NAAAVGQAAH	179 ALLVRGSADG	119 AFASFRVVSG	185 SADGAFLD

56 AWPLIGNAAA	178 VALLVRGSAD	115 ADRPAFASFR	183 RGSADGAF
510 TIKPKSFKVN	176 ELVALLVRGS	93 PIVVLNGERA	181 LVRGSADG
455 DLTSRVMIFS	163 RQVLEGHVLS	70 AHLSFARLAR	180 LLVRGSAD
412 YHIPKDTVVF	158 RQPRSRQVLE	13 LNPLSIQQTT	178 VALLVRGS
379 PYVLAFLYEA	155 FFTRQPRSRQ	439 NFDPARFLDK	161 RSRQVLEG
349 YPDVQTRVQA	148 AHSMMRNFFT	402 ATTANTSVLG	151 MMRNFFTR
283 LRPGAAPRDM	147 AAHSMMRNFF	229 EEFGRTVGAG	148 AHSMMRNF
278 RHCESLRPGA	143 VQRRAAHSMM	200 AVANVMSAVC	144 QRRAAHSM
247 LQYFPNPVRT	138 SEHWKVQRRA	186 ADGAFLDPRP	117 RPAFASFR
207 AVCFGCRYSH	131 SMAFGHYSEH	174 ARELVALLVR	116 DRPAFASF
201 VANVMSAVCF	127 SGGRSMAFGH	126 VSGGRSMAFG	115 ADRPAFAS
191 LDPRPLTVVA	125 VVSGGRSMAF	118 PAFASFRVVS	112 SAFADRPA
178 VALLVRGSAD	124 RVVSGGRSMA	100 ERAIHQALVQ	107 LVQQGSAF
175 RELVALLVRG	123 FRVVSGGRSM	89 LGSCPIVVLN	106 ALVQQGSA
151 MMRNFFTRQP	120 FASFRVVSGG	77 LARRYGDVFQ	88 RLGSCPIV
125 VVSGGRSMAF	119 AFASFRVVSG	43 RRRQLRSAPP	80 RYGDVFQI
124 RVVSGGRSMA	118 PAFASFRVVS	521 TLRESMELLD	58 PLIGNAAA
104 HQALVQQGSA	112 SAFADRPAFA	514 KSFKVNVTLR	57 WPLIGNAA
91 SCPIVVLNGE	106 ALVQQGSAFA	488 AHQCDFRANP	51 PPGPFAWP
90 GSCPIVVLNG	102 AIHQALVQQG	457 TSRVMIFSVG	50 APPGPFAW
89 LGSCPIVVLN	99 GERAIHQALV	415 PKDTVVFVNQ	49 SAPPGPFA
77 LARRYGDVFQ	95 VVLNGERAIH	403 TTANTSVLGY	48 RSAPPGPF
61 GNAAAVGQAA	91 SCPIVVLNGE	397 VTIPHATTAN	43 RRRQLRSA
51 PPGPFAWPLI	88 RLGSCPIVVL	391 FSSFVPVTIP	42 QRRRQLRS
34 HVGQRLLRQR	84 VFQIRLGSCP	371 CMGDQPNLPY	38 RLLRQRRR
33 VHVGQRLLRQ	78 ARRYGDVFQI	356 VQAELDQVVG	25 LLLSVLAT
13 LNPLSIQQTT	74 FARLARRYGD	353 QTRVQAELDQ	15 PLSIQQTT
529 LDSAVQNLQA	56 AWPLIGNAAA	327 IFGASQDTLS	14 NPLSIQQT
516 FKVNVTLRES	50 APPGPFAWPL	322 ATITDIFGAS	12 PLNPLSIQ
505 FSYGLTIKPK	38 RLLRQRRRQL	310 GGGARLDLEN	483 FISILAHQ
501 AKMNFSYGLT	35 VGQRLLRQRR	305 AGDSHGGGAR	413 HIPKDTVV
487 LAHQCDFRAN	28 SVLATVHVGQ	303 KAAGDSHGGG	401 HATTANTS
476 SKMQLFLFIS	25 LLLSVLATVH	282 SLRPGAAPRD	382 LAFLYEAM
464 SVGKRRCIGE	533 VQNLQAKETC	280 CESLRPGAAP	357 QAELDQVV
454 KDLTSRVMIF	532 AVQNLQAKET	276 FLRHCESLRP	329 GASQDTLS
440 FDPARFLDKD	517 KVNVTLRESM	272 ILDKFLRHCE	296 FILSAEKK
437 PENFDPARFL	516 FKVNVTLRES	257 VFREFEQLNR	236 GAGSLVDV
434 WPNPENFDPA	513 PKSFKVNVTL	253 PVRTVFREFE	199 VAVANVMS
402 ATTANTSVLG	508 GLTIKPKSFK	213 RYSHDDPEFR	114 FADRPAFA
382 LAFLYEAMRF	493 FRANPNEPAK	204 VMSAVCFGCR	105 QALVQQGS
375 QPNLPYVLAF	492 DFRANPNEPA	202 ANVMSAVCFG	93 PIVVLNGE
362 QVVGRDRLPC	486 ILAHQCDFRA	185 SADGAFLDPR	69 AAHLSFAR
359 ELDQVVGRDR	483 FISILAHQCD	184 GSADGAFLDP	63 AAAVGQAA
356 VQAELDQVVG	470 CIGEELSKMQ	183 RGSADGAFLD	55 FAWPLIGN
345 LFTRYPDVQT	466 GKRRCIGEEL	136 HYSEHWKVQR	30 LATVHVGQ

289 PRDMMDAFIL	465 VGKRRCIGEE	113 AFADRPAFAS	524 ESMELLDS
287 AAPRDMMDAF	462 IFSVGKRRCI	108 VQQGSAFADR	494 RANPNEPA
242 DVMPWLQYFP	454 KDLTSRVMIF	90 GSCPIVVLNG	487 LAHQCDFR
240 LVDVMPWLQY	452 INKDLTSRVM	79 RRYGDVFQIR	461 MIFSVGKR
236 GAGSLVDVMP	450 GLINKDLTSR	64 AAVGQAAHLS	451 LINKDLTS
233 RTVGAGSLVD	433 KWPNPENFDP	62 NAAAVGQAAH	404 TANTSVLG
193 PRPLTVVAVA	431 PLKWPNPENF	58 PLIGNAAAVG	398 TIPHATTA
159 QPRSRQVLEG	430 DPLKWPNPEN	48 RSAPPGPFAW	326 DIFGASQD
147 AAHSMMRNFF	427 VNHDPLKWPN	42 QRRRQLRSAP	323 TITDIFGA
132 MAFGHYSEHW	420 VFVNQWSVNH	33 VHVGQRLLRQ	304 AAGDSHGG
123 FRVVSGGRSM	416 KDTVVFVNQW	515 SFKVNVTLRE	303 KAAGDSHG
107 LVQQGSAFAD	413 HIPKDTVVFV	510 TIKPKSFKVN	294 DAFILSAE
105 QALVQQGSAF	411 GYHIPKDTVV	505 FSYGLTIKPK	287 AAPRDMMD
74 FARLARRYGD	401 HATTANTSVL	504 NFSYGLTIKP	226 SHNEEFGR
54 PFAWPLIGNA	400 PHATTANTSV	493 FRANPNEPAK	147 AAHSMMRN
53 GPFAWPLIGN	395 VPVTIPHATT	480 LFLFISILAH	146 RAAHSMMR
47 LRSAPPGPFA	394 FVPVTIPHAT	468 RRCIGEELSK	132 MAFGHYSE
27 LSVLATVHVG	387 EAMRFSSFVP	467 KRRCIGEELS	118 PAFASFRV
530 DSAVQNLQAK	383 AFLYEAMRFS	463 FSVGKRRCIG	102 AIHQALVQ
522 LRESMELLDS	368 RLPCMGDQPN	459 RVMIFSVGKR	101 RAIHQALV
514 KSFKVNVTLR	363 VVGRDRLPCM	444 RFLDKDGLIN	68 QAAHLSFA
465 VGKRRCIGEE	360 LDQVVGRDRL	428 NHDPLKWPNP	64 AAVGQAAH
452 INKDLTSRVM	355 RVQAELDQVV	424 QWSVNHDPLK	62 NAAAVGQA
432 LKWPNPENFD	350 PDVQTRVQAE	408 SVLGYHIPKD	59 LIGNAAAV
431 PLKWPNPENF	348 RYPDVQTRVQ	387 EAMRFSSFVP	525 SMELLDSA
419 VVFVNQWSVN	343 LLLFTRYPDV	383 AFLYEAMRFS	506 SYGLTIKP
414 IPKDTVVFVN	341 WLLLLFTRYP	370 PCMGDQPNLP	471 IGEELSKM
396 PVTIPHATTA	326 DIFGASQDTL	366 RDRLPCMGDQ	356 VQAELDQV
324 ITDIFGASQD	323 TITDIFGASQ	358 AELDQVVGRD	227 HNEEFGRT
312 GARLDLENVP	312 GARLDLENVP	357 QAELDQVVGR	167 EGHVLSEA
309 HGGGARLDLE	306 GDSHGGGARL	348 RYPDVQTRVQ	162 SRQVLEGH
294 DAFILSAEKK	303 KAAGDSHGGG	346 FTRYPDVQTR	136 HYSEHWKV
277 LRHCESLRPG	297 ILSAEKKAAG	331 SQDTLSTALQ	533 VQNLQAKE
267 NFSNFILDKF	296 FILSAEKKAA	312 GARLDLENVP	484 ISILAHQC
266 RNFSNFILDK	288 APRDMMDAFI	309 HGGGARLDLE	472 GEELSKMQ
250 FPNPVRTVFR	287 AAPRDMMDAF	302 KKAAGDSHGG	462 IFSVGKRR
237 AGSLVDVMPW	285 PGAAPRDMMD	300 AEKKAAGDSH	458 SRVMIFSV
225 LSHNEEFGRT	283 LRPGAAPRDM	292 MMDAFILSAE	435 PNPENFDP
206 SAVCFGCRYS	280 CESLRPGAAP	290 RDMMDAFILS	426 SVNHDPLK
203 NVMSAVCFGC	278 RHCESLRPGA	281 ESLRPGAAPR	419 VVFVNQWS
202 ANVMSAVCFG	271 FILDKFLRHC	270 NFILDKFLRH	408 SVLGYHIP
197 TVVAVANVMS	264 LNRNFSNFIL	266 RNFSNFILDK	394 FVPVTIPH
174 ARELVALLVR	263 QLNRNFSNFI	260 EFEQLNRNFS	393 SFVPVTIP
148 AHSMMRNFFT	259 REFEQLNRNF	242 DVMPWLQYFP	331 SQDTLSTA

146 RAAHSMMRNF	254 VRTVFREFEQ	240 LVDVMPWLQY	318 ENVPATIT
138 SEHWKVQRRA	253 PVRTVFREFE	236 GAGSLVDVMP	315 LDLENVPA
113 AFADRPAFAS	251 PNPVRTVFRE	230 EFGRTVGAGS	281 ESLRPGAA
81 YGDVFQIRLG	243 VMPWLQYFPN	227 HNEEFGRTVG	278 RHCESLRP
70 AHLSFARLAR	241 VDVMPWLQYF	220 EFRELLSHNE	260 EFEQLNRN
507 YGLTIKPKSF	236 GAGSLVDVMP	211 GCRYSHDDPE	259 REFEQLNR
506 SYGLTIKPKS	231 FGRTVGAGSL	207 AVCFGCRYSH	238 GSLVDVMP
503 MNFSYGLTIK	230 EFGRTVGAGS	197 TVVAVANVMS	232 GRTVGAGS
493 FRANPNEPAK	224 LLSHNEEFGR	179 ALLVRGSADG	230 EFGRTVGA
482 LFISILAHQC	223 ELLSHNEEFG	176 ELVALLVRGS	221 FRELLSHN
458 SRVMIFSVGK	222 RELLSHNEEF	175 RELVALLVRG	215 SHDDPEFR
448 KDGLINKDLT	210 FGCRYSHDDP	164 QVLEGHVLSE	198 VVAVANVM
416 KDTVVFVNQW	201 VANVMSAVCF	163 RQVLEGHVLS	172 SEARELVA
406 NTSVLGYHIP	199 VAVANVMSAV	158 RQPRSRQVLE	168 GHVLSEAR
399 IPHATTANTS	191 LDPRPLTVVA	151 MMRNFFTRQP	150 SMMRNFFT
374 DQPNLPYVLA	186 ADGAFLDPRP	150 SMMRNFFTRQ	139 EHWKVQRR
353 QTRVQAELDQ	181 LVRGSADGAF	145 RRAAHSMMRN	134 FGHYSEHW
325 TDIFGASQDT	180 LLVRGSADGA	144 QRRAAHSMMR	131 SMAFGHYS
317 LENVPATITD	177 LVALLVRGSA	140 HWKVQRRAAH	123 FRVVSGGR
302 KKAAGDSHGG	152 MRNFFTRQPR	133 AFGHYSEHWK	104 HQALVQQG
299 SAEKKAAGDS	144 QRRAAHSMMR	130 RSMAFGHYSE	94 IVVLNGER
293 MDAFILSAEK	140 HWKVQRRAAH	128 GGRSMAFGHY	91 SCPIVVLN
256 TVFREFEQLN	139 EHWKVQRRAA	120 FASFRVVSGG	73 SFARLARR
241 VDVMPWLQYF	135 GHYSEHWKVQ	102 AIHQALVQQG	28 SVLATVHV
229 EEFGRTVGAG	133 AFGHYSEHWK	101 RAIHQALVQQ	2 GTSLSPND
228 NEEFGRTVGA	132 MAFGHYSEHW	82 GDVFQIRLGS	530 DSAVQNLQ
194 RPLTVVAVAN	129 GRSMAFGHYS	74 FARLARRYGD	526 MELLDSAV
184 GSADGAFLDP	113 AFADRPAFAS	71 HLSFARLARR	520 VTLRESME
143 VQRRAAHSMM	105 QALVQQGSAF	67 GQAAHLSFAR	518 VNVTLRES
137 YSEHWKVQRR	93 PIVVLNGERA	59 LIGNAAAVGQ	517 KVNVTLRE
126 VSGGRSMAFG	92 CPIVVLNGER	49 SAPPGPFAWP	516 FKVNVTLR
108 VQQGSAFADR	85 FQIRLGSCPI	44 RRQLRSAPPG	511 IKPKSFKV
48 RSAPPGPFAW	75 ARLARRYGDV	39 LLRQRRRQLR	505 FSYGLTIK
32 TVHVGQRLLR	71 HLSFARLARR	32 TVHVGQRLLR	493 FRANPNEP
6 SPNDPWPLNP	66 VGQAAHLSFA	28 SVLATVHVGQ	489 HQCDFRAN
2 GTSLSPNDPW	63 AAAVGQAAHL	2 GTSLSPNDPW	460 VMIFSVGK
533 VQNLQAKETC	61 GNAAAVGQAA	530 DSAVQNLQAK	453 NKDLTSRV
526 MELLDSAVQN	60 IGNAAAVGQA	526 MELLDSAVQN	448 KDGLINKD

491 CDFRANPNEP	47 LRSAPPGPFA	525 SMELLDSAVQ	443 ARFLDKDG
488 AHQCDFRANP	46 QLRSAPPGPF	522 LRESMELLDS	427 VNHDPLKW
484 ISILAHQCDF	42 QRRRQLRSAP	506 SYGLTIKPKS	424 QWSVNHDP
449 DGLINKDLTS	37 QRLLRQRRRQ	497 PNEPAKMNFS	422 VNQWSVNH
444 RFLDKDGLIN	30 LATVHVGQRL	495 ANPNEPAKMN	421 FVNQWSVN
430 DPLKWPNPEN	26 LLSVLATVHV	490 QCDFRANPNE	420 VFVNQWSV
391 FSSFVPVTIP	24 LLLLSVLATV	487 LAHQCDFRAN	417 DTVVFVNQ
378 LPYVLAFLYE		485 SILAHQCDFR	416 KDTVVFVN
331 SQDTLSTALQ	HLA-A26 Nonamers	483 FISILAHQCD	411 GYHIPKDT
319 NVPATITDIF		464 SVGKRRCIGE	406 NTSVLGYH
310 GGGARLDLEN	Pos 123456789	458 SRVMIFSVGK	397 VTIPHATT
284 RPGAAPRDMM	242 DVMPWLQYF	449 DGLINKDLTS	391 FSSFVPVT
279 HCESLRPGAA	455 DLTSRVMIF	445 FLDKDGLINK	383 AFLYEAMR
258 FREFEQLNRN	470 CIGEELSKM	438 ENFDPARFLD	379 PYVLAFLY
257 VFREFEQLNR	223 ELLSHNEEF	435 PNPENFDPAR	373 GDQPNLPY
222 RELLSHNEEF	260 EFEQLNRNF	432 LKWPNPENFD	365 GRDRLPCM
218 DPEFRELLSH	256 TVFREFEQL	425 WSVNHDPLKW	363 VVGRDRLP
212 CRYSHDDPEF	253 PVRTVFREF	420 VFVNQWSVNH	361 DQVVGRDR
208 VCFGCRYSHD	528 LLDSAVQNL	416 KDTVVFVNQW	360 LDQVVGRD
136 HYSEHWKVQR	341 WLLLLFTRY	406 NTSVLGYHIP	352 VQTRVQAE
130 RSMAFGHYSE	263 QLNRNFSNF	392 SSFVPVTIPH	340 QWLLLLFT
121 ASFRVVSGGR	521 TLRESMELL	381 VLAFLYEAMR	327 IFGASQDT
118 PAFASFRVVS	479 QLFLFISIL	368 RLPCMGDQPN	324 ITDIFGAS
115 ADRPAFASFR	474 ELSKMQLFL	364 VGRDRLPCMG	311 GGARLDLE
111 GSAFADRPAF	473 EELSKMQLF	359 ELDQVVGRDR	309 HGGGARLD
110 QGSAFADRPA	413 HIPKDTVVF	350 PDVQTRVQAE	306 GDSHGGGA
92 CPIVVLNGER	381 VLAFLYEAM	342 LLLLFTRYPD	295 AFILSAEK
73 SFARLARRYG	338 ALQWLLLLF	340 QWLLLLFTRY	279 HCESLRPG
67 GQAAHLSFAR	377 NLPYVLAFL	332 QDTLSTALQW	268 FSNFILDK
45 RQLRSAPPGP	351 DVQTRVQAE	324 ITDIFGASQD	258 FREFEQLN
19 QQTTLLLLLS	239 SLVDVMPWL	307 DSHGGGARLD	241 VDVMPWLQ
496 NPNEPAKMNF	173 EARELVALL	301 EKKAAGDSHG	237 AGSLVDVM
492 DFRANPNEPA	106 ALVQQGSAF	298 LSAEKKAAGD	235 VGAGSLVD
468 RRCIGEELSK	22 TLLLLLSVL	293 MDAFILSAEK	222 RELLSHNE
463 FSVGKRRCIG	417 DTVVFVNQW	285 PGAAPRDMMD	216 HDDPEFRE
439 NFDPARFLDK	359 ELDQVVGRD	246 WLQYFPNPVR	210 FGCRYSHD
428 NHDPLKWPNP	334 TLSTALQWL	224 LLSHNEEFGR	208 VCFGCRYS
425 WSVNHDPLKW	326 DIFGASQDT	223 ELLSHNEEFG	205 MSAVCFGC
420 VFVNQWSVNH	220 EFRELLSHN	217 DDPEFRELLS	204 VMSAVCFG
417 DTVVFVNQWS	176 ELVALLVRG	208 VCFGCRYSHD	196 LTVVAVAN
392 SSFVPVTIPH	520 VTLRESMEL	167 EGHVLSEARE	193 PRPLTVVA
385 LYEAMRFSSF	508 GLTIKPKSF	166 LEGHVLSEAR	182 VRGSADGA
383 AFLYEAMRFS	485 SILAHQCDF	160 PRSRQVLEGH	177 LVALLVRG
367 DRLPCMGDQP	336 STALQWLLL	153 RNFFTRQPRS	175 RELVALLV
320 VPATITDIFG	169 HVLSEAREL	152 MRNFFTRQPR	169 HVLSEARE
305 AGDSHGGGAR	124 RVVSGGRSM	149 HSMMRNFFTR	163 RQVLEGHV
300 AEKKAAGDSH	83 DVFQIRLGS	132 MAFGHYSEHW	155 FFTRQPRS
280 CESLRPGAAP	31 ATVHVGQRL	129 GRSMAFGHYS	135 GHYSEHWK
275 KFLRHCESLR	499 EPAKMNFSY	122 SFRVVSGGRS	129 GRSMAFGH

270 NFILDKFLRH	402 ATTANTSVL	121 ASFRVVSGGR	125 VVSGGRSM
269 SNFILDKFLR	73 SFARLARRY	103 IHQALVQQGS	111 GSAFADRP
261 FEQLNRNFSN	17 SIQQTTLLL	96 VLNGERAIHQ	108 VQQGSAFA
259 REFEQLNRNF	527 ELLDSAVQN	95 VVLNGERAIH	103 IHQALVQQ
221 FRELLSHNEE	383 AFLYEAMRF	73 SFARLARRYG	95 VVLNGERA
214 YSHDDPEFRE	333 DTLSTALQW	52 PGPFAWPLIG	85 FQIRLGSC
186 ADGAFLDPRP	307 DSHGGGARL	45 RQLRSAPPGP	81 YGDVFQIR
166 LEGHVLSEAR	197 TVVAVANVM	40 LRQRRRQLRS	66 VGQAAHLS
154 NFFTRQPRSR	115 ADRPAFASF	36 GQRLLRQRRR	61 GNAAAVGQ
149 HSMMRNFFTR	39 LLRQRRRQL	29 VLATVHVGQR	60 IGNAAAVG
139 EHWKVQRRAA	32 TVHVGQRLL	27 LSVLATVHVG	56 AWPLIGNA
133 AFGHYSEHWK	438 ENFDPARFL	25 LLLSVLATVH	35 VGQRLLRQ
127 SGGRSMAFGH	394 FVPVTIPHA	19 QQTTLLLLLS	27 LSVLATVH
103 IHQALVQQGS	386 YEAMRFSSF	534 QNLQAKETCQ	21 TTLLLLLS
79 RRYGDVFQIR	376 PNLPYVLAF	531 SAVQNLQAKE	13 LNPLSIQQ
72 LSFARLARRY	322 ATITDIFGA	528 LLDSAVQNLQ	10 PWPLNPLS
40 LRQRRRQLRS	271 FILDKFLRH	508 GLTIKPKSFK	
5 LSPNDPWPLN	230 EFGRTVGAG	503 MNFSYGLTIK	HLA-B8 Nonamers
3 TSLSPNDPWP	217 DDPEFRELL	498 NEPAKMNFSY	
534 QNLQAKETCQ	200 AVANVMSAV	489 HQCDFRANPN	Pos 123456789
515 SFKVNVTLRE	177 LVALLVRGS	481 FLFISILAHQ	39 LLRQRRRQL
498 NEPAKMNFSY	102 AIHQALVQQ	476 SKMQLFLFIS	173 EARELVALL
489 HQCDFRANPN	15 PLSIQQTTL	470 CIGEELSKMQ	521 TLRESMELL
427 VNHDPLKWPN	481 FLFISILAH	455 DLTSRVMIFS	510 TIKPKSFKV
422 VNQWSVNHDP	475 LSKMQLFLF	450 GLINKDLTSR	508 GLTIKPKSF
387 EAMRFSSFVP	451 LINKDLTSR	440 FDPARFLDKD	455 DLTSRVMIF
365 GRDRLPCMGD	404 TANTSVLGY	433 KWPNPENFDP	159 QPRSRQVLE
364 VGRDRLPCMG	374 DQPNLPYVL	429 HDPLKWPNPE	465 VGKRRCIGE
350 PDVQTRVQAE	323 TITDIFGAS	427 VNHDPLKWPN	414 IPKDTVVFV
340 QWLLLLFTRY	288 APRDMMDAF	421 FVNQWSVNHD	288 APRDMMDAF
327 IFGASQDTLS	216 HDDPEFREL	419 VVFVNQWSVN	479 QLFLFISIL
273 LDKFLRHCES	196 LTVVAVANV	407 TSVLGYHIPK	474 ELSKMQLFL
254 VRTVFREFEQ	147 AAHSMMRNF	384 FLYEAMRFSS	473 EELSKMQLF
252 NPVRTVFREF	34 HVGQRLLRQ	367 DRLPCMGDQP	431 PLKWPNPEN
249 YFPNPVRTVF	21 TTLLLLLSV	365 GRDRLPCMGD	239 SLVDVMPWL
244 MPWLQYFPNP	517 KVNVTLRES	344 LLFTRYPDVQ	99 GERAIHQAL
219 PEFRELLSHN	510 TIKPKSFKV	341 WLLLLFTRYP	528 LLDSAVQNL
217 DDPEFRELLS	482 LFISILAHQ	323 TITDIFGASQ	512 KPKSFKVNV
205 MSAVCFGCRY	447 DKDGLINKD	317 LENVPATITD	467 KRRCIGEEL
163 RQVLEGHVLS	380 YVLAFLYEA	299 SAEKKAAGDS	463 FSVGKRRCI
160 PRSRQVLEGH	361 DQVVGRDRL	277 LRHCESLRPG	450 GLINKDLTS
158 RQPRSRQVLE	355 RVQAELDQV	275 KFLRHCESLR	377 NLPYVLAFL
145 RRAAHSMMRN	344 LLFTRYPDV	265 NRNFSNFILD	86 QIRLGSCPI
141 WKVQRRAAHS	327 IFGASQDTL	251 PNPVRTVFRE	22 TLLLLLSVL
140 HWKVQRRAAH	319 NVPATITDI	243 VMPWLQYFPN	535 NLQAKETCQ
129 GRSMAFGHYS	316 DLENVPATI	209 CFGCRYSHDD	475 LSKMQLFLF
122 SFRVVSGGRS	275 KFLRHCESL	205 MSAVCFGCRY	444 RFLDKDGLI
82 GDVFQIRLGS	272 ILDKFLRHC	203 NVMSAVCFGC	334 TLSTALQWL

43 RRRQLRSAPP	268 FSNFILDKF	178 VALLVRGSAD	299 SAEKKAAGD
37 QRLLRQRRRQ	203 NVMSAVCFG	155 FFTRQPRSRQ	223 ELLSHNEEF
11 WPLNPLSIQQ	172 SEARELVAL	141 WKVQRRAAHS	188 GAFLDPRPL
518 VNVTLRESME	165 VLEGHVLSE	137 YSEHWKVQRR	179 ALLVRGSAD
504 NFSYGLTIKP	129 GRSMAFGHY	135 GHYSEHWKVQ	126 VSGGRSMAF
495 ANPNEPAKMN	69 AAHLSFARL	131 SMAFGHYSEH	77 LARRYGDVF
467 KRRCIGEELS	20 QTTLLLLLS	127 SGGRSMAFGH	51 PPGPFAWPL
436 NPENFDPARF	524 ESMELLDSA	109 QQGSAFADRP	17 SIQQTTLLL
435 PNPENFDPAR	509 LTIKPKSFK	107 LVQQGSAFAD	15 PLSIQQTTL
433 KWPNPENFDP	497 PNEPAKMNF	81 YGDVFQIRLG	364 VGRDRLPCM
429 HDPLKWPNPE	461 MIFSVGKRR	72 LSFARLARRY	271 FILDKFLRH
424 QWSVNHDPLK	456 LTSRVMIFS	37 QRLLRQRRRQ	190 FLDPRPLTV
370 PCMGDQPNLP	409 VLGYHIPKD	35 VGQRLLRQRR	120 FASFRVVSG
348 RYPDVQTRVQ	397 VTIPHATTA	34 HVGQRLLRQR	69 AAHLSFARL
307 DSHGGGARLD	384 FLYEAMRFS	8 NDPWPLNPLS	515 SFKVNVTLR
290 RDMMDAFILS	364 VGRDRLPCM	5 LSPNDPWPLN	500 PAKMNFSYG
281 ESLRPGAAPR	236 GAGSLVDVM	3 TSLSPNDPWP	386 YEAMRFSSF
253 PVRTVFREFE	181 LVRGSADGA		344 LLFTRYPDV
251 PNPVRTVFRE	126 VSGGRSMAF	HLA-B*1510 Nonamers	337 TALQWLLLL
227 HNEEFGRTVG	125 VVSGGRSMA		282 SLRPGAAPR
210 FGCRYSHDDP	112 SAFADRPAF	Pos 123456789	218 DPEFRELLS
209 CFGCRYSHDD	58 PLIGNAAAV	148 AHSMMRNFF	172 SEARELVAL
153 RNFFTRQPRS	28 SVLATVHVG	89 LGSCPIVVL	76 RLARRYGDV
135 GHYSEHWKVQ	25 LLLSVLATV	139 EHWKVQRRA	64 AAVGQAAHL
128 GGRSMAFGHY	24 LLLLSVLAT	438 ENFDPARFL	41 RQRRRQLRS
84 VFQIRLGSCP	532 AVQNLQAKE	412 YHIPKDTVV	448 KDGLINKDL
44 RRQLRSAPPG	492 DFRANPNEP	361 DQVVGRDRL	336 STALQWLLL
42 QRRRQLRSAP	432 LKWPNPENF	216 HDDPEFREL	331 SQDTLSTAL
36 GQRLLRQRRR	421 FVNQWSVNH	32 TVHVGQRLL	320 VPATITDIF
35 VGQRLLRQRR	419 VVFVNQWSV	514 KSFKVNVTL	298 LSAEKKAAG
10 PWPLNPLSIQ	337 TALQWLLLL	308 SHGGGARLD	286 GAAPRDMMD
8 NDPWPLNPLS	324 ITDIFGASQ	307 DSHGGGARL	276 FLRHCESLR
499 EPAKMNFSYG	233 RTVGAGSLV	215 SHDDPEFRE	269 SNFILDKFL
497 PNEPAKMNFS	198 VVAVANVMS	188 GAFLDPRPL	253 PVRTVFREF
438 ENFDPARFLD	164 QVLEGHVLS	172 SEARELVAL	250 FPNPVRTVF
415 PKDTVVFVNQ	156 FTRQPRSRQ	81 YGDVFQIRL	192 DPRPLTVVA
361 DQVVGRDRLP	89 LGSCPIVVL	39 LLRQRRRQL	140 HWKVQRRAA
285 PGAAPRDMMD	76 RLARRYGDV	521 TLRESMELL	138 SEHWKVQRR
262 EQLNRNFSNF	64 AAVGQAAHL	488 AHQCDFRAN	112 SAFADRPAF
167 EGHVLSEARE	19 QQTTLLLLL	474 ELSKMQLFL	106 ALVQQGSAF
260 EFEQLNRNFS	8 NDPWPLNPL	472 GEELSKMQL	520 VTLRESMEL
52 PGPFAWPLIG	519 NVTLRESME	428 NHDPLKWPN	514 KSFKVNVTL
301 EKKAAGDSHG	514 KSFKVNVTL	424 QWSVNHDPL	485 SILAHQCDF
	483 FISILAHQC	402 ATTANTSVL	472 GEELSKMQL
HLA-A*0201 Octamers	459 RVMIFSVGK	374 DQPNLPYVL	438 ENFDPARFL
	441 DPARFLDKD	327 IFGASQDTL	429 HDPLKWPNP
Pos 12345678	437 PENFDPARF	278 RHCESLRPG	413 HIPKDTVVF
531 SAVQNLQA	408 SVLGYHIPK	239 SLVDVMPWL	352 VQTRVQAEL
525 SMELLDSA	406 NTSVLGYHI	232 GRTVGAGSL	338 ALQWLLLLF
494 RANPNEPA	403 TTANTSVLG	226 SHNEEFGRT	316 DLENVPATI

488 AHQCDFRA
481 FLFISILA
436 NPENFDPA
398 TIPHATTA
395 VPVTIPHA
381 VLAFLYEA
376 PNLPYVLA
351 DVQTRVQA
331 SQDTLSTA
323 TITDIFGA
315 LDLENVPA
306 GDSHGGGA
298 LSAEKKAA
297 ILSAEKKA
293 MDAFILSA
288 APRDMMDA
281 ESLRPGAA
280 CESLRPGA
230 EFGRTVGA
200 AVANVMSA
195 PLTVVAVA
193 PRPLTVVA
182 VRGSADGA
179 ALLVRGSA
172 SEARELVA
167 EGHVLSEA
141 WKVQRRAA
140 HWKVQRRA
126 VSGGRSMA
114 FADRPAFA
112 SAFADRPA
108 VQQGSAFA
106 ALVQQGSA
99 GERAIHQA
95 VVLNGERA
71 HLSFARLA
68 QAAHLSFA
63 AAAVGQAA
62 NAAAVGQA
58 PLIGNAAA
57 WPLIGNAA
56 AWPLIGNA
49 SAPPGPFA
43 RRRQLRSA
24 LLLLSVLA

398 TIPHATTAN
390 RFSSFVPVT
372 MGDQPNLPY
370 PCMGDQPNL
367 DRLPCMGDQ
362 QVVGRDRLP
346 FTRYPDVQT
296 FILSAEKKA
250 FPNPVRTVF
229 EEFGRTVGA
213 RYSHDDPEF
209 CFGCRYSHD
202 ANVMSAVCF
182 VRGSADGAF
142 KVQRRAAHS
107 LVQQGSAFA
93 PIVVLNGER
54 PFAWPLIGN
18 IQQTTLLLL
16 LSIQQTTLL
12 PLNPLSIQQ
515 SFKVNVTLR
495 ANPNEPAKM
472 GEELSKMQL
464 SVGKRRCIG
450 GLINKDLTS
443 ARFLDKDGL
431 PLKWPNPEN
426 SVNHDPLKW
418 TVVFVNQWS
396 PVTIPHATT
378 LPYVLAFLY
353 QTRVQAELD
331 SQDTLSTAL
320 VPATITDIF
294 DAFILSAEK
291 DMMDAFILS
282 SLRPGAAPR
269 SNFILDKFL
255 RTVFREFEQ
249 YFPNPVRTV
241 VDVMPWLQY
240 LVDVMPWLQ
206 SAVCFGCRY
190 FLDPRPLTV
158 RQPRSRQVL

173 EARELVALL
169 HVLSEAREL
168 GHVLSEARE
158 RQPRSRQVL
103 IHQALVQQG
22 TLLLLLSVL
400 PHATTANTS
370 PCMGDQPNL
337 TALQWLLLL
334 TLSTALQWL
309 HGGGARLDL
217 DDPEFRELL
163 RQVLEGHVL
99 GERAIHQAL
70 AHLSFARLA
69 AAHLSFARL
51 PPGPFAWPL
33 VHVGQRLLR
31 ATVHVGQRL
18 IQQTTLLLL
15 PLSIQQTTL
528 LLDSAVQNL
520 VTLRESMEL
479 QLFLFISIL
467 KRRCIGEEL
443 ARFLDKDGL
413 HIPKDTVVF
352 VQTRVQAEL
336 STALQWLLL
331 SQDTLSTAL
260 EFEQLNRNF
256 TVFREFEQL
250 FPNPVRTVF
183 RGSADGAFL
135 GHYSEHWKV
64 AAVGQAAHL
17 SIQQTTLLL
16 LSIQQTTLL
8 NDPWPLNPL
5 LSPNDPWPL
501 AKMNFSYGL
497 PNEPAKMNF
462 IFSVGKRRC
453 NKDLTSRVM
448 KDGLINKDL
432 LKWPNPENF

312 GARLDLENV
301 EKKAAGDSH
264 LNRNFSNFI
263 QLNRNFSNF
232 GRTVGAGSL
217 DDPEFRELL
216 HDDPEFREL
169 HVLSEAREL
115 ADRPAFASF
89 LGSCPIVVL
74 FARLARRYG
46 QLRSAPPGP
513 PKSFKVNVT
452 INKDLTSRV
443 ARFLDKDGL
442 PARFLDKDG
424 QWSVNHDPL
361 DQVVGRDRL
327 IFGASQDTL
309 HGGGARLDL
265 NRNFSNFIL
262 EQLNRNFSN
229 EEFGRTVGA
163 RQVLEGHVL
81 YGDVFQIRL
32 TVHVGQRLL
18 IQQTTLLLL
501 AKMNFSYGL
498 NEPAKMNFS
464 SVGKRRCIG
446 LDKDGLINK
412 YHIPKDTVV
402 ATTANTSVL
374 DQPNLPYVL
370 PCMGDQPNL
351 DVQTRVQAE
335 LSTALQWLL
307 DSHGGGARL
300 AEKKAAGDS
290 RDMMDAFIL
280 CESLRPGAA
275 KFLRHCESL
274 DKFLRHCES
273 LDKFLRHCE
256 TVFREFEQL
251 PNPVRTVFR

HLA-A*0202 Nonamers

Pos 123456789
535 NLQAKETCQ
529 LDSAVQNLQ
498 NEPAKMNFS
492 DFRANPNEP
485 SILAHQCDF
440 FDPARFLDK
402 ATTANTSVL
399 IPHATTANT
385 LYEAMRFSS

96 VLNGERAIH
95 VVLNGERAI
94 IVVLNGERA
84 VFQIRLGSC
66 VGQAAHLSF
65 AVGQAAHLS
59 LIGNAAAVG
46 QLRSAPPGP
29 VLATVHVGQ
4 SLSPNDPWP
2 GTSLSPNDP
518 VNVTLRESM

377 NLPYVLAFL
376 PNLPYVLAF
335 LSTALQWLL
290 RDMMDAFIL
275 KFLRHCESL
269 SNFILDKFL
265 NRNFSNFIL
236 GAGSLVDVM
19 QQTTLLLLL
437 PENFDPARF
288 APRDMMDAF
285 PGAAPRDMM

220 EFRELLSHN
183 RGSADGAFL
158 RQPRSRQVL
149 HSMMRNFFT
147 AAHSMMRNF
97 LNGERAIHQ
31 ATVHVGQRL
19 QQTTLLLLL
16 LSIQQTTLL
8 NDPWPLNPL
5 LSPNDPWPL
527 ELLDSAVQN

380 YVLAFLYEA	504 NFSYGLTIK	284 RPGAAPRDM	519 NVTLRESME
355 RVQAELDQV	486 ILAHQCDFR	253 PVRTVFREF	499 EPAKMNFSY
335 LSTALQWLL	445 FLDKDGLIN	213 RYSHDDPEF	496 NPNEPAKMN
327 IFGASQDTL	368 RLPCMGDQP	197 TVVAVANVM	481 FLFISILAH
319 NVPATITDI	363 VVGRDRLPC	147 AAHSMMRNF	466 GKRRCIGEE
310 GGGARLDLE	352 VQTRVQAEL	124 RVVSGGRSM	440 FDPARFLDK
302 KKAAGDSHG	314 RLDLENVPA	112 SAFADRPAF	409 VLGYHIPKD
301 EKKAAGDSH	309 HGGGARLDL	47 LRSAPPGPF	384 FLYEAMRFS
297 ILSAEKKAA	295 AFILSAEKK	508 GLTIKPKSF	359 ELDQVVGRD
292 MMDAFILSA	285 PGAAPRDMM	473 EELSKMQLF	346 FTRYPDVQT
285 PGAAPRDMM	267 NFSNFILDK	386 YEAMRFSSF	314 RLDLENVPA
284 RPGAAPRDM	259 REFEQLNRN	383 AFLYEAMRF	310 GGGARLDLE
234 TVGAGSLVD	234 TVGAGSLVD	381 VLAFLYEAM	297 ILSAEKKAA
204 VMSAVCFGC	207 AVCFGCRYS	364 VGRDRLPCM	260 EFEQLNRNF
199 VAVANVMSA	195 PLTVVAVAN	248 QYFPNPVRT	257 VFREFEQLN
197 TVVAVANVM	192 DPRPLTVVA	242 DVMPWLQYF	255 RTVFREFEQ
186 ADGAFLDPR	188 GAFLDPRPL	223 ELLSHNEEF	195 PLTVVAVAN
183 RGSADGAFL	187 DGAFLDPRP	202 ANVMSAVCF	176 ELVALLVRG
176 ELVALLVRG	179 ALLVRGSAD	126 VSGGRSMAF	170 VLSEARELV
171 LSEARELVA	170 VLSEARELV	115 ADRPAFASF	141 WKVQRRAAH
145 RRAAHSMMR	154 NFFTRQPRS	106 ALVQQGSAF	122 SFRVVSGGR
144 QRRAAHSMM	148 AHSMMRNFF	77 LARRYGDVF	84 VFQIRLGSC
130 RSMAFGHYS	144 QRRAAHSMM	518 VNVTLRESM	44 RRQLRSAPP
118 PAFASFRVV	132 MAFGHYSEH	495 ANPNEPAKM	37 QRLLRQRRR
116 DRPAFASFR	99 GERAIHQAL	470 CIGEELSKM	34 HVGQRLLRQ
112 SAFADRPAF	86 QIRLGSCPI	455 DLTSRVMIF	24 LLLLSVLAT
110 QGSAFADRP	81 YGDVFQIRL	320 VPATITDIF	490 QCDFRANPN
103 IHQALVQQG	77 LARRYGDVF	263 QLNRNFSNF	476 SKMQLFLFI
99 GERAIHQAL	51 PPGPFAWPL	182 VRGSADGAF	457 TSRVMIFSV
75 ARLARRYGD	47 LRSAPPGPF	485 SILAHQCDF	395 VPVTIPHAT
72 LSFARLARR	38 RLLRQRRRQ	475 LSKMQLFLF	391 FSSFVPVTI
67 GQAAHLSFA	23 LLLLLSVLA	414 IPKDTVVFV	381 VLAFLYEAM
66 VGQAAHLSF	9 DPWPLNPLS	349 YPDVQTRVQ	376 PNLPYVLAF
62 NAAAVGQAA	535 NLQAKETCQ	338 ALQWLLLLF	375 QPNLPYVLA
61 GNAAAVGQA	530 DSAVQNLQA	268 FSNFILDKF	362 QVVGRDRLP
60 IGNAAAVGQ	501 AKMNFSYGL	249 YFPNPVRTV	211 GCRYSHDDP
53 GPFAWPLIG	467 KRRCIGEEI	192 DPRPLTVVA	209 CFGCRYSHD
47 LRSAPPGPF	453 NKDLTSRVM	144 QRRAAHSMM	182 VRGSADGAF
28 SVLATVHVG	439 NFDPARFLD	143 VQRRAAHSM	171 LSEARELVA
	389 MRFSSFVPV	119 AFASFRVVS	165 VLEGHVLSE
HLA-A*0202 Decamers	335 LSTALQWLL	90 GSCPIVVLN	157 TRQPRSRQV
	297 ILSAEKKAA	66 VGQAAHLSF	154 NFFTRQPRS
Pos 1234567890	276 FLRHCESLR	511 IKPKSFKVN	142 KVQRRAAHS
63 AAAVGQAAHL	274 DKFLRHCES	494 RANPNEPAK	113 AFADRPAFA
303 KAAGDSHGGG	265 NRNFSNFIL	452 INKDLTSRV	95 VVLNGERAI
286 GAAPRDMMDA	257 VFREFEQLN	391 FSSFVPVTI	78 ARRYGDVFQ
146 RAAHSMMRNF	235 VGAGSLVDV	390 RFSSFVPVT	75 ARLARRYGD
68 QAAHLSFARL	232 GRTVGAGSL	373 GDQPNLPYV	72 LSFARLARR
62 NAAAVGQAAH	183 RGSADGAFL	359 ELDQVVGRD	71 HLSFARLAR
200 AVANVMSAVC	180 LLVRGSADG	357 QAELDQVVG	57 WPLIGNAAA
119 AFASFRVVSG	143 VQRRAAHSM	347 TRYPDVQTR	40 LRQRRRQLR
113 AFADRPAFAS	119 AFASFRVVS	315 LDLENVPAT	36 GQRLLRQRR
530 DSAVQNLQAK	113 AFADRPAFA	297 ILSAEKKAA	29 VLATVHVGQ
499 EPAKMNFSYG	88 RLGSCPIVV	272 ILDKFLRHC	23 LLLLLSVLA
493 FRANPNEPAK	71 HLSFARLAR	228 NEEFGRTVG	6 SPNDPWPLN

486 ILAHQCDFRA	26 LLSVLATVH	227 HNEEFGRTV	4 SLSPNDPWP
441 DPARFLDKDG	5 LSPNDPWPL	176 ELVALLVRG	531 SAVQNLQAK
403 TTANTSVLGY	460 VMIFSVGKR	157 TRQPRSRQV	492 DFRANPNEP
400 PHATTANTSV	448 KDGLINKDL	156 FTRQPRSRQ	486 ILAHQCDFR
386 YEAMRFSSFV	444 RFLDKDGLI	140 HWKVQRRAA	454 KDLTSRVMI
381 VLAFLYEAMR	424 QWSVNHDPL	137 YSEHWKVQR	445 FLDKDGLIN
356 VQAELDQVVG	420 VFVNQWSVN	94 IVVLNGERA	436 NPENFDPAR
336 STALQWLLLL	393 SFVPVTIPH	73 SFARLARRY	434 WPNPENFDP
328 FGASQDTLST	358 AELDQVVGR	49 SAPPGPFAW	405 NTSVLGYHI
320 VPATITDIFG	343 LLLFTRYPD	48 RSAPPGPFA	399 IPHATTANT
311 GGARLDLENV	342 LLLLFTRYP	38 RLLRQRRRQ	383 AFLYEAMRF
304 AAGDSHGGGA	318 ENVPATITD	4 SLSPNDPWP	378 LPYVLAFLY
302 KKAAGDSHGG	315 LDLENVPAT	527 ELLDSAVQN	366 RDRLPCMGD
298 LSAEKKAAGD	301 EKKAAGDSH	517 KVNVTLRES	353 QTRVQAELD
293 MDAFILSAEK	290 RDMMDAFIL	513 PKSFKVNVT	349 YPDVQTRVQ
287 AAPRDMMDAF	284 RPGAAPRDM	471 IGEELSKMQ	342 LLLLFTRYP
285 PGAAPRDMMD	281 ESLRPGAAP	463 FSVGKRRCI	341 WLLLLFTRY
235 VGAGSLVDVM	270 NFILDKFLR	411 GYHIPKDTV	319 NVPATITDI
205 MSAVCFGCRY	246 WLQYFPNPV	403 TTANTSVLG	272 ILDKFLRHC
198 VVAVANVMSA	224 LLSHNEEFG	384 FLYEAMRFS	268 FSNFILDKF
187 DGAFLDPRPL	189 AFLDPRPLT	358 AELDQVVGR	252 NPVRTVFRE
184 GSADGAFLDP	167 EGHVLSEAR	356 VQAELDQVV	246 WLQYFPNPV
177 LVALLVRGSA	163 RQVLEGHVL	350 PDVQTRVQA	244 MPWLQYFPN
172 SEARELVALL	155 FFTRQPRSR	318 ENVPATITD	231 FGRTVGAGS
147 AAHSMMRNFF	146 RAAHSMMRN	306 GDSHGGGAR	213 RYSHDDPEF
145 RRAAHSMMRN	139 EHWKVQRRA	298 LSAEKKAAG	202 ANVMSAVCF
131 SMAFGHYSEH	121 ASFRVVSGG	286 GAAPRDMMD	194 RPLTVVAVA
117 RPAFASFRVV	116 DRPAFASFR	283 LRPGAAPRD	156 FTRQPRSRQ
111 GSAFADRPAF	100 ERAIHQALV	247 LQYFPNPVR	143 VQRRAAHSM
104 HQALVQQGSA	72 LSFARLARR	235 VGAGSLVDV	128 GGRSMAFGH
100 ERAIHQALVQ	55 FAWPLIGNA	234 TVGAGSLVD	96 VLNGERAIH
76 RLARRYGDVF	50 APPGPFAWP	229 EEFGRTVGA	93 PIVVLNGER
73 SFARLARRYG	13 LNPLSIQQT	198 VVAVANVMS	92 CPIVVLNGE
69 AAHLSFARLA	531 SAVQNLQAK	195 PLTVVAVAN	79 RRYGDVFQI
67 GQAAHLSFAR	511 IKPKSFKVN	193 PRPLTVVAV	66 VGQAAHLSF
64 AAVGQAAHLS	462 IFSVGKRRC	190 FLDPRPLTV	58 PLIGNAAAV
61 GNAAAVGQAA	446 LDKDGLINK	189 AFLDPRPLT	53 GPFAWPLIG
54 PFAWPLIGNA	435 PNPENFDPA	187 DGAFLDPRP	49 SAPPGPFAW
48 RSAPPGPFAW	430 DPLKWPNPE	184 GSADGAFLD	43 RRRQLRSAP
29 VLATVHVGQR	414 IPKDTVVFV	177 LVALLVRGS	26 LLSVLATVH
531 SAVQNLQAKE	387 EAMRFSSFV	164 QVLEGHVLS	10 PWPLNPLSI
500 PAKMNFSYGL	373 GDQPNLPYV	146 RAAHSMMRN	9 DPWPLNPLS
494 RANPNEPAKM	347 TRYPDVQTR	136 HYSEHWKVQ	503 MNFSYGLTI
487 LAHQCDFRAN	293 MDAFILSAE	125 VVSGGRSMA	497 PNEPAKMNF
442 PARFLDKDGL	278 RHCESLRPG	120 FASFRVVSG	478 MQLFLFISI
404 TANTSVLGYH	266 RNFSNFILD	118 PAFASFRVV	470 CIGEELSKM
401 HATTANTSVL	262 EQLNRNFSN	111 GSAFADRPA	441 DPARFLDKD
387 EAMRFSSFVP	245 PWLQYFPNP	95 VVLNGERAI	437 PENFDPARF
382 LAFLYEAMRF	226 SHNEEFGRT	87 IRLGSCPIV	432 LKWPNPENF
357 QAELDQVVGR	219 PEFRELLSH	82 GDVFQIRLG	430 DPLKWPNPE
337 TALQWLLLLF	193 PRPLTVVAV	63 AAAVGQAAH	401 HATTANTSV
329 GASQDTLSTA	185 SADGAFLDP	60 IGNAAAVGQ	388 AMRFSSFVP
321 PATITDIFGA	138 SEHWKVQRR	37 QRLLRQRRR	387 EAMRFSSFV
312 GARLDLENVP	133 AFGHYSEHW	36 GQRLLRQRR	369 LPCMGDQPN
299 SAEKKAAGDS	122 SFRVVSGGR	26 LLSVLATVH	368 RLPCMGDQP
294 DAFILSAEKK	118 PAFASFRVV	534 QNLQAKETC	357 QAELDQVVG

236 GAGSLVDVMP	103 IHQALVQQG	531 SAVQNLQAK	343 LLLFTRYPD
206 SAVCFGCRYS	92 CPIVVLNGE	515 SFKVNVTLR	296 FILSAEKKA
201 VANVMSAVCF	90 GSCPIVVLN	512 KPKSFKVNV	289 PRDMMDAFI
199 VAVANVMSAV	79 RRYGDVFQI	510 TIKPKSFKV	284 RPGAAPRDM
188 GAFLDPRPLT	500 PAKMNFSYG	509 LTIKPKSFK	242 DVMPWLQYF
185 SADGAFLDPR	498 NEPAKMNFS	507 YGLTIKPKS	236 GAGSLVDVM
178 VALLVRGSAD	480 LFLFISILA	499 EPAKMNFSY	224 LLSHNEEFG
173 EARELVALLV	478 MQLFLFISI	492 DFRANPNEP	206 SAVCFGCRY
132 MAFGHYSEHW	476 SKMQLFLFI	487 LAHQCDFRA	201 VANVMSAVC
120 FASFRVVSGG	449 DGLINKDLT	486 ILAHQCDFR	199 VAVANVMSA
118 PAFASFRVVS	422 VNQWSVNHD	466 GKRRCIGEE	185 SADGAFLDP
114 FADRPAFASF	416 KDTVVFVNQ	457 TSRVMIFSV	181 LVRGSADGA
112 SAFADRPAFA	392 SSFVPVTIP	454 KDLTSRVMI	180 LLVRGSADG
105 QALVQQGSAF	345 LFTRYPDVQ	439 NFDPARFLD	178 VALLVRGSA
101 RAIHQALVQQ	330 ASQDTLSTA	436 NPENFDPAR	161 RSRQVLEGH
77 LARRYGDVFQ	298 LSAEKKAAG	431 PLKWPNPEN	151 MMRNFFTRQ
74 FARLARRYGD	292 MMDAFILSA	421 FVNQWSVNH	148 AHSMMRNFF
55 FAWPLIGNAA	287 AAPRDMMDA	416 KDTVVFVNQ	144 QRRAAHSMM
49 SAPPGPFAWP	248 QYFPNPVRT	415 PKDTVVFVN	117 RPAFASFRV
30 LATVHVGQRL	218 DPEFRELLS	397 VTIPHATTA	114 FADRPAFAS
532 AVQNLQAKET	199 VAVANVMSA	394 FVPVTIPHA	88 RLGSCPIVV
501 AKMNFSYGLT	166 LEGHVLSEA	392 SSFVPVTIP	63 AAAVGQAAH
495 ANPNEPAKMN	161 RSRQVLEGH	375 QPNLPYVLA	55 FAWPLIGNA
488 AHQCDFRANP	160 PRSRQVLEG	367 DRLPCMGDQ	52 PGPFAWPLI
443 ARFLDKDGLI	127 SGGRSMAFG	362 QVVGRDRLP	50 APPGPFAWP
405 ANTSVLGYHI	120 FASFRVVSG	360 LDQVVGRDR	47 LRSAPPGPF
402 ATTANTSVLG	109 QQGSAFADR	348 RYPDVQTRV	42 QRRRQLRSA
388 AMRFSSFVPV	91 SCPIVVLNG	346 FTRYPDVQT	38 RLLRQRRRQ
383 AFLYEAMRFS	80 RYGDVFQIR	345 LFTRYPDVQ	30 LATVHVGQR
358 AELDQVVGRD	67 GQAAHLSFA	329 GASQDTLST	25 LLLSVLATV
338 ALQWLLLLFT	61 GNAAAVGQA	323 TITDIFGAS	14 NPLSIQQTT
330 ASQDTLSTAL	42 QRRRQLRSA	316 DLENVPATI	12 PLNPLSIQQ
322 ATITDIFGAS	35 VGQRLLRQR	313 ARLDLENVP	11 WPLNPLSIQ
313 ARLDLENVPA	513 PKSFKVNVT	311 GGARLDLEN	506 SYGLTIKPK
305 AGDSHGGGAR	502 KMNFSYGLT	282 SLRPGAAPR	494 RANPNEPAK
300 AEKKAAGDSH	488 AHQCDFRAN	281 ESLRPGAAP	483 FISILAHQC
295 AFILSAEKKA	469 RCIGEELSK	280 CESLRPGAA	461 MIFSVGKRR
288 APRDMMDAFI	466 GKRRCIGEE	279 HCESLRPGA	404 TANTSVLGY
237 AGSLVDVMPW	458 SRVMIFSVG	271 FILDKFLRH	398 TIPHATTAN
207 AVCFGCRYSH	457 TSRVMIFSV	259 REFEQLNRN	382 LAFLYEAMR
202 ANVMSAVCFG	452 INKDLTSRV	252 NPVRTVFRE	329 GASQDTLST
189 AFLDPRPLTV	440 FDPARFLDK	251 PNPVRTVFR	323 TITDIFGAS
186 ADGAFLDPRP	427 VNHDPLKWP	238 GSLVDVMPW	294 DAFILSAEK
179 ALLVRGSADG	415 PKDTVVFVN	237 AGSLVDVMP	132 MAFGHYSEH
174 ARELVALLVR	412 YHIPKDTVV	230 EFGRTVGAG	105 QALVQQGSA
148 AHSMMRNFFT	405 ANTSVLGYH	214 YSHDDPEFR	102 AIHQALVQQ
133 AFGHYSEHWK	375 QPNLPYVLA	207 AVCFGCRYS	68 QAAHLSFAR
121 ASFRVVSGGR	356 VQAELDQVV	201 VANVMSAVC	62 NAAAVGQAA
115 ADRPAFASFR	340 QWLLLLFTR	200 AVANVMSAV	533 VQNLQAKET
106 ALVQQGSAFA	339 LQWLLLLFT	194 RPLTVVAVA	525 SMELLDSAV
102 AIHQALVQQG	312 GARLDLENV	191 LDPRPLTVV	524 ESMELLDSA
78 ARRYGDVFQI	286 GAAPRDMMD	175 RELVALLVR	487 LAHQCDFRA
75 ARLARRYGDV	283 LRPGAAPRD	171 LSEARELVA	471 IGEELSKMQ
70 AHLSFARLAR	252 NPVRTVFRE	170 VLSEARELV	451 LINKDLTSR
65 AVGQAAHLSF	244 MPWLQYFPN	167 EGHVLSEAR	392 SSFVPVTIP
56 AWPLIGNAAA	238 GSLVDVMPW	165 VLEGHVLSE	326 DIFGASQDT
50 APPGPFAWPL	208 VCFGCRYSH	160 PRSRQVLEG	321 PATITDIFG
31 ATVHVGQRLL	205 MSAVCFGCR	155 FFTRQPRSR	315 LDLENVPAT

HLA-A*0203 Nonamers

Pos	1 2 3 4 5 6 7 8 9
62	N A A A V G Q A A
113	A F A D R P A F A
530	D S A V Q N L Q A
493	F R A N P N E P A
287	A A P R D M M D A
111	G S A F A D R P A
67	G Q A A H L S F A
61	G N A A A V G Q A
48	R S A P P G P F A
487	L A H Q C D F R A
199	V A V A N V M S A
178	V A L L V R G S A
105	Q A L V Q Q G S A
55	F A W P L I G N A
330	A S Q D T L S T A
322	A T I T D I F G A
305	A G D S H G G G A
70	A H L S F A R L A
56	A W P L I G N A A
524	E S M E L L D S A
480	L F L F I S I L A
435	P N P E N F D P A
397	V T I P H A T T A
394	F V P V T I P H A
380	Y V L A F L Y E A
375	Q P N L P Y V L A
350	P D V Q T R V Q A
314	R L D L E N V P A
297	I L S A E K K A A
296	F I L S A E K K A
292	M M D A F I L S A
280	C E S L R P G A A
279	H C E S L R P G A
229	E E F G R T V G A
194	R P L T V V A V A
192	D P R P L T V V A
181	L V R G S A D G A
171	L S E A R E L V A
166	L E G H V L S E A
140	H W K V Q R R A A
139	E H W K V Q R R A
125	V V S G G R S M A
107	L V Q Q G S A F A
98	N G E R A I H Q A
94	I V V L N G E R A
57	W P L I G N A A A
42	Q R R R Q L R S A
23	L L L L L S V L A
63	A A A V G Q A A H
303	K A A G D S H G G
286	G A A P R D M M D
146	R A A H S M M R N
68	Q A A H L S F A R
200	A V A N V M S A V

194	R P L T V V A V A
191	L D P R P L T V V
151	M M R N F F T R Q
98	N G E R A I H Q A
82	G D V F Q I R L G
30	L A T V H V G Q R
11	W P L N P L S I Q
523	R E S M E L L D S
512	K P K S F K V N V
506	S Y G L T I K P K
505	F S Y G L T I K P
494	R A N P N E P A K
491	C D F R A N P N E
477	K M Q L F L F I S
471	I G E E L S K M Q
429	H D P L K W P N P
428	N H D P L K W P N
407	T S V L G Y H I P
382	L A F L Y E A M R
379	P Y V L A F L Y E
325	T D I F G A S Q D
310	G G G A R L D L E
303	K A A G D S H G G
299	S A E K K A A G D
279	H C E S L R P G A
186	A D G A F L D P R
175	R E L V A L L V R
150	S M M R N F F T R
108	V Q Q G S A F A D
87	I R L G S C P I V
85	F Q I R L G S C P
49	S A P P G P F A W
48	R S A P P G P F A
43	R R R Q L R S A P
7	P N D P W P L N P
1	M G T S L S P N D
525	S M E L L D S A V
503	M N F S Y G L T I
496	N P N E P A K M N
489	H Q C D F R A N P
484	I S I L A H Q C D
463	F S V G K R R C I
454	K D L T S R V M I
365	G R D R L P C M G
350	P D V Q T R V Q A
348	R Y P D V Q T R V
328	F G A S Q D T L S
311	G G A R L D L E N
305	A G D S H G G G A
304	A A G D S H G G G
302	K K A A G D S H G
215	S H D D P E F R E
168	G H V L S E A R E
157	T R Q P R S R Q V
153	R N F F T R Q P R
145	R R A A H S M M R
141	W K V Q R R A A H
140	H W K V Q R R A A

154	N F F T R Q P R S
141	W K V Q R R A A H
138	S E H W K V Q R R
123	F R V V S G G R S
117	R P A F A S F R V
113	A F A D R P A F A
110	Q G S A F A D R P
102	A I H Q A L V Q Q
88	R L G S C P I V V
78	A R R Y G D V F Q
74	F A R L A R R Y G
71	H L S F A R L A R
61	G N A A A V G Q A
58	P L I G N A A A V
55	F A W P L I G N A
43	R R R Q L R S A P
34	H V G Q R L L R Q
29	V L A T V H V G Q
28	S V L A T V H V G
9	D P W P L N P L S
7	P N D P W P L N P
6	S P N D P W P L N
2	G T S L S P N D P
530	D S A V Q N L Q A
526	M E L L D S A V Q
525	S M E L L D S A V
524	E S M E L L D S A
516	F K V N V T L R E
504	N F S Y G L T I K
496	N P N E P A K M N
493	F R A N P N E P A
489	H Q C D F R A N P
484	I S I L A H Q C D
481	F L F I S I L A H
464	S V G K R R C I G
461	M I F S V G K R R
459	R V M I F S V G K
458	S R V M I F S V G
456	L T S R V M I F S
450	G L I N K D L T S
449	D G L I N K D L T
447	D K D G L I N K D
446	L D K D G L I N K
435	P N P E N F D P A
434	W P N P E N F D P
430	D P L K W P N P E
427	V N H D P L K W P
420	V F V N Q W S V N
419	V V F V N Q W S V
417	D T V V F V N Q W
409	V L G Y H I P K D
407	T S V L G Y H I P
406	N T S V L G Y H I
404	T A N T S V L G Y
399	I P H A T T A N T
398	T I P H A T T A N
396	P V T I P H A T T
395	V P V T I P H A T

304	A A G D S H G G G
303	K A A G D S H G G
287	A A P R D M M D A
230	E F G R T V G A G
226	S H N E E F G R T
198	V V A V A N V M S
193	P R P L T V V A V
167	E G H V L S E A R
146	R A A H S M M R N
136	H Y S E H W K V Q
118	P A F A S F R V V
101	R A I H Q A L V Q
59	L I G N A A A V G
394	F V P V T I P H A
356	V Q A E L D Q V V
281	E S L R P G A A P
238	G S L V D V M P W
227	H N E E F G R T V
164	Q V L E G H V L S
162	S R Q V L E G H V
91	S C P I V V L N G
90	G S C P I V V L N
28	S V L A T V H V G
530	D S A V Q N L Q A
517	K V N V T L R E S
511	I K P K S F K V N
493	F R A N P N E P A
484	I S I L A H Q C D
462	I F S V G K R R C
460	V M I F S V G K R
458	S R V M I F S V G
435	P N P E N F D P A
427	V N H D P L K W P
426	S V N H D P L K W
422	V N Q W S V N H D
421	F V N Q W S V N H
419	V V F V N Q W S V
417	D T V V F V N Q W
416	K D T V V F V N Q
408	S V L G Y H I P K
393	S F V P V T I P H
358	A E L D Q V V G R
318	E N V P A T I T D
311	G G A R L D L E N
308	S H G G G A R L D
306	G D S H G G G A R
278	R H C E S L R P G
261	F E Q L N R N F S
259	R E F E Q L N R N
254	V R T V F R E F E
237	A G S L V D V M P
235	V G A G S L V D V
222	R E L L S H N E E
221	F R E L L S H N E
215	S H D D P E F R E
196	L T V V A V A N V
177	L V A L L V R G S
168	G H V L S E A R E

119 AFASFRVVS	104 HQALVQQGS	393 SFVPVTIPH	160 PRSRQVLEG
499 EPAKMNFSY	101 RAIHQALVQ	389 MRFSSFVPV	150 SMMRNFFTR
486 ILAHQCDFR	97 LNGERAIHQ	388 AMRFSSFVP	139 EHWKVQRRA
441 DPARFLDKD	68 QAAHLSFAR	385 LYEAMRFSS	134 FGHYSEHWK
403 TTANTSVLG	63 AAAVGQAAH	380 YVLAFLYEA	131 SMAFGHYSE
400 PHATTANTS	62 NAAAVGQAA	372 MGDQPNLPY	127 SGGRSMAFG
386 YEAMRFSSF	36 GQRLLRQRR	371 CMGDQPNLP	123 FRVVSGGRS
381 VLAFLYEAM	33 VHVGQRLLR	365 GRDRLPCMG	108 VQQGSAFAD
356 VQAELDQVV	533 VQNLQAKET	354 TRVQAELDQ	104 HQALVQQGS
336 STALQWLLL	507 YGLTIKPKS	351 DVQTRVQAE	103 IHQALVQQG
328 FGASQDTLS	487 LAHQCDFRA	342 LLLLFTRYP	100 ERAIHQALV
320 VPATITDIF	465 VGKRRCIGE	341 WLLLLFTRY	94 IVVLNGERA
311 GGARLDLEN	436 NPENFDPAR	330 ASQDTLSTA	82 GDVFQIRLG
304 AAGDSHGGG	434 WPNPENFDP	325 TDIFGASQD	73 SFARLARRY
302 KKAAGDSHG	399 IPHATTANT	324 ITDIFGASQ	61 GNAAAVGQA
298 LSAEKKAAG	371 CMGDQPNLP	317 LENVPATIT	60 IGNAAAVGQ
293 MDAFILSAE	366 RDRLPCMGD	314 RLDLENVPA	56 AWPLIGNAA
285 PGAAPRDMM	349 YPDVQTRVQ	303 KAAGDSHGG	27 LSVLATVHV
235 VGAGSLVDV	332 QDTLSTALQ	302 KKAAGDSHG	13 LNPLSIQQT
205 MSAVCFGCR	329 GASQDTLST	299 SAEKKAAGD	2 GTSLSPNDP
198 VVAVANVMS	313 ARLDLENVP	293 MDAFILSAE	526 MELLDSAVQ
187 DGAFLDPRP	308 SHGGGARLD	277 LRHCESLRP	518 VNVTLRESM
184 GSADGAFLD	300 AEKKAAGDS	267 NFSNFILDK	516 FKVNVTLRE
177 LVALLVRGS	289 PRDMMDAFI	261 FEQLNRNFS	505 FSYGLTIKP
172 SEARELVAL	273 LDKFLRHCE	254 VRTVFREFE	504 NFSYGLTIK
147 AAHSMMRNF	251 PNPVRTVFR	245 PWLQYFPNP	491 CDFRANPNE
145 RRAAHSMMR	243 VMPWLQYFP	240 LVDVMPWLQ	489 HQCDFRANP
131 SMAFGHYSE	237 AGSLVDVMP	224 LLSHNEEFG	488 AHQCDFRAN
117 RPAFASFRV	231 FGRTVGAGS	220 EFRELLSHN	477 KMQLFLFIS
104 HQALVQQGS	227 HNEEFGRTV	208 VCFGCRYSH	459 RVMIFSVGK
100 ERAIHQALV	222 RELLSHNEE	206 SAVCFGCRY	453 NKDLTSRVM
76 RLARRYGDV	221 FRELLSHNE	205 MSAVCFGCR	447 DKDGLINKD
73 SFARLARRY	184 GSADGAFLD	199 VAVANVMSA	423 NQWSVNHDP
69 AAHLSFARL	162 SRQVLEGHV	196 LTVVAVANV	420 VFVNQWSVN
64 AAVGQAAHL	159 QPRSRQVLE	179 ALLVRGSAD	418 TVVFVNQWS
54 PFAWPLIGN	137 YSEHWKVQR	159 QPRSRQVLE	415 PKDTVVFVN
29 VLATVHVGQ	136 HYSEHWKVQ	152 MRNFFTRQP	411 GYHIPKDTV
531 SAVQNLQAK	135 GHYSEHWKV	151 MMRNFFTRQ	410 LGYHIPKDT
500 PAKMNFSYG	131 SMAFGHYSE	150 SMMRNFFTR	407 TSVLGYHIP
494 RANPNEPAK	128 GGRSMAFGH	132 MAFGHYSEH	403 TTANTSVLG
442 PARFLDKDG	123 FRVVSGGRS	131 SMAFGHYSE	397 VTIPHATTA
404 TANTSVLGY	117 RPAFASFRV	129 GRSMAFGHY	390 RFSSFVPVT
401 HATTANTSV	114 FADRPAFAS	114 FADRPAFAS	389 MRFSSFVPV
387 EAMRFSSFV	105 QALVQQGSA	108 VQQGSAFAD	380 YVLAFLYEA
382 LAFLYEAMR	60 IGNAAAVGQ	107 LVQQGSAFA	379 PYVLAFLYE
357 QAELDQVVG	57 WPLIGNAAA	101 RAIHQALVQ	373 GDQPNLPYV
337 TALQWLLLL	56 AWPLIGNAA	100 ERAIHQALV	372 MGDQPNLPY
329 GASQDTLST	53 GPFAWPLIG	98 NGERAIHQA	365 GRDRLPCMG
321 PATITDIFG	52 PGPFAWPLI	96 VLNGERAIH	363 VVGRDRLPC
312 GARLDLENV	45 RQLRSAPPG	93 PIVVLNGER	360 LDQVVGRDR
299 SAEKKAAGD	27 LSVLATVHV	83 DVFQIRLGS	350 PDVQTRVQA
294 DAFILSAEK	14 NPLSIQQTT	79 RRYGDVFQI	347 TRYPDVQTR
236 GAGSLVDVM	10 PWPLNPLSI	72 LSFARLARR	340 QWLLLLFTR
206 SAVCFGCRY	6 SPNDPWPLN	68 QAAHLSFAR	339 LQWLLLLFT
201 VANVMSAVC	534 QNLQAKETC	67 GQAAHLSFA	332 QDTLSTALQ
188 GAFLDPRPL	526 MELLDSAVQ	62 NAAAVGQAA	328 FGASQDTLS
185 SADGAFLDP	522 LRESMELLD	59 LIGNAAAVG	324 ITDIFGASQ
173 EARELVALL	516 FKVNVTLRE	57 WPLIGNAAA	322 ATITDIFGA
132 MAFGHYSEH	493 FRANPNEPA	54 PFAWPLIGN	317 LENVPATIT

120 FASFRVVSG
118 PAFASFRVV
114 FADRPAFAS
112 SAFADRPAF
101 RAIHQALVQ
77 LARRYGDVF
74 FARLARRYG
49 SAPPGPFAW
30 LATVHVGQR
532 AVQNLQAKE
501 AKMNFSYGL
495 ANPNEPAKM
488 AHQCDFRAN
443 ARFLDKDGL
405 ANTSVLGYH
402 ATTANTSVL
388 AMRFSSFVP
383 AFLYEAMRF
358 AELDQVVGR
338 ALQWLLLLF
313 ARLDLENVP
300 AEKKAAGDS
295 AFILSAEKK
288 APRDMMDAF
237 AGSLVDVMP
207 AVCFGCRYS
202 ANVMSAVCF
189 AFLDPRPLT
186 ADGAFLDPR
179 ALLVRGSAD
174 ARELVALLV
148 AHSMMRNFF
133 AFGHYSEHW
121 ASFRVVSGG
115 ADRPAFASF
106 ALVQQGSAF
102 AIHQALVQQ
78 ARRYGDVFQ
75 ARLARRYGD
65 AVGQAAHLS
50 APPGPFAWP
31 ATVHVGQRL

HLA-A*0203 Decamers

Pos 1234567890
56 AWPLIGNAAA
296 FILSAEKKAA

279 HCESLRPGAA
139 EHWKVQRRAA

61 GNAAAVGQAA
55 FAWPLIGNAA
193 PRPLTVVAVA
112 SAFADRPAFA
106 ALVQQGSAFA
297 ILSAEKKAAG

490 QCDFRANPN
442 PARFLDKDG
433 KWPNPENFD
425 WSVNHDPLK
423 NQWSVNHDP
401 HATTANTSV
400 PHATTANTS
395 VPVTIPHAT
391 FSSFVPVTI
388 AMRFSSFVP
385 LYEAMRFSS
369 LPCMGDQPN
357 QAELDQVVG
354 TRVQAELDQ
306 GDSHGGGAR
280 CESLRPGAA
277 LRHCESLRP
258 FREFEQLNR
247 LQYFPNPVR
225 LSHNEEFGR
214 YSHDDPEFR
212 CRYSHDDPE
211 GCRYSHDDP
204 VMSAVCFGC
201 VANVMSAVC
178 VALLVRGSA
152 MRNFFTRQP
134 FGHYSEHWK
111 GSAFADRPA
110 QGSAFADRP
78 ARRYGDVFQ
75 ARLARRYGD
70 AHLSFARLA
44 RRQLRSAPP
41 RQRRRQLRS
40 LRQRRRQLR
37 QRLLRQRRR
3 TSLSPNDPW

HLA-A26 Decamers

Pos 1234567890
333 DTLSTALQWL

527 ELLDSAVQNL
474 ELSKMQLFLF
326 DIFGASQDTL
403 TTANTSVLGY
351 DVQTRVQAEL

125 VVSGGRSMAF
83 DVFQIRLGSC

380 YVLAFLYEAM
363 VVGRDRLPCM
336 STALQWLLLL
255 RTVFREFEQL
181 LVRGSADGAF
21 TTLLLLLSVL

53 GPFAWPLIG
50 APPGPFAWP
46 QLRSAPPGP
42 QRRRQLRSA
41 RQRRRQLRS
35 VGQRLLRQR
30 LATVHVGQR
27 LSVLATVHV
24 LLLLSVLAT
23 LLLLLSVLA
12 PLNPLSIQQ
10 PWPLNPLSI
3 TSLSPNDPW
533 VQNLQAKET
529 LDSAVQNLQ
523 RESMELLDS
522 LRESMELLD
506 SYGLTIKPK
505 FSYGLTIKP
503 MNFSYGLTI
500 PAKMNFSYG
498 NEPAKMNFS
491 CDFRANPNE
483 FISILAHQC
476 SKMQLFLFI
469 RCIGEELSK
468 RRCIGEELS
460 VMIFSVGKR
451 LINKDLTSR
445 FLDKDGLIN
444 RFLDKDGLI
441 DPARFLDKD
433 KWPNPENFD
429 HDPLKWPNP
426 SVNHDPLKW
425 WSVNHDPLK
422 VNQWSVNHD
418 TVVFVNQWS
410 LGYHIPKDT
408 SVLGYHIPK
387 EAMRFSSFV
378 LPYVLAFLY
369 LPCMGDQPN

366 RDRLPCMGD
363 VVGRDRLPC
353 QTRVQAELD
344 LLFTRYPDV
343 LLLFTRYPD

340 QWLLLLFTR
328 FGASQDTLS

326 DIFGASQDT
322 ATITDIFGA
319 NVPATITDI
312 GARLDLENV
310 GGGARLDLE
304 AAGDSHGGG

295 AFILSAEKK
293 MDAFILSAE
292 MMDAFILSA
279 HCESLRPGA
270 NFILDKFLR
267 NFSNFILDK
258 FREFEQLNR
249 YFPNPVRTV
248 QYFPNPVRT
247 LQYFPNPVR
243 VMPWLQYFP
241 VDVMPWLQY
240 LVDVMPWLQ
210 FGCRYSHDD
208 VCFGCRYSH
205 MSAVCFGCR
204 VMSAVCFGC
203 NVMSAVCFG
200 AVANVMSAV
184 GSADGAFLD
175 RELVALLVR
174 ARELVALLV
166 LEGHVLSEA
155 FFTRQPRSR
137 YSEHWKVQR
135 GHYSEHWKV
129 GRSMAFGHY
125 VVSGGRSMA
121 ASFRVVSGG
119 AFASFRVVS
111 GSAFADRPA
98 NGERAIHQA
87 IRLGSCPIV
85 FQIRLGSCP
67 GQAAHLSFA
35 VGQRLLRQR
33 VHVGQRLLR
21 TTLLLLLSV
20 QTTLLLLLS
3 TSLSPNDPW

280 CESLRPGAAP	17 SIQQTTLLLL	301 EKKAAGDSH
140 HWKVQRRAAH	520 VTLRESMELL	300 AEKKAAGDS
62 NAAAVGQAAH	262 EQLNRNFSNF	294 DAFILSAEK
57 WPLIGNAAAV	240 LVDVMPWLQY	292 MMDAFILSA
529 LDSAVQNLQA	88 RLGSCPIVVL	291 DMMDAFILS
523 RESMELLDSA	65 AVGQAAHLSF	287 AAPRDMMDA
492 DFRANPNEPA	319 NVPATITDIF	274 DKFLRHCES
486 ILAHQCDFRA	267 NFSNFILDKF	273 LDKFLRHCE
479 QLFLFISILA	519 NVTLRESMEL	270 NFILDKFLR
434 WPNPENFDPA	431 PLKWPNPENF	266 RNFSNFILD
396 PVTIPHATTA	517 KVNVTLRESM	262 EQLNRNFSN
393 SFVPVTIPHA	455 DLTSRVMIFS	258 FREFEQLNR
379 PYVLAFLYEA	377 NLPYVLAFLY	257 VFREFEQLN
374 DQPNLPYVLA	176 ELVALLVRGS	255 RTVFREFEQ
349 YPDVQTRVQA	142 KVQRRAAHSM	246 WLQYFPNPV
329 GASQDTLSTA	76 RLARRYGDVF	241 VDVMPWLQY
321 PATITDIFGA	46 QLRSAPPGPF	233 RTVGAGSLV
313 ARLDLENVPA	469 RCIGEELSKM	222 RELLSHNEE
304 AAGDSHGGGA	408 SVLGYHIPKD	221 FRELLSHNE
295 AFILSAEKKA	242 DVMPWLQYFP	218 DPEFRELLS
291 DMMDAFILSA	196 LTVVAVANVM	211 GCRYSHDDP
286 GAAPRDMMDA	31 ATVHVGQRLL	204 VMSAVCFGC
278 RHCESLRPGA	4 SLSPNDPWPL	203 NVMSAVCFG
228 NEEFGRTVGA	510 TIKPKSFKVN	185 SADGAFLDP
198 VVAVANVMSA	447 DKDGLINKDL	181 LVRGSADGA
191 LDPRPLTVVA	417 DTVVFVNQWS	180 LLVRGSADG
180 LLVRGSADGA	413 HIPKDTVVFV	178 VALLVRGSA
177 LVALLVRGSA	322 ATITDIFGAS	174 ARELVALLV
170 VLSEARELVA	274 DKFLRHCESL	166 LEGHVLSEA
165 VLEGHVLSEA	249 YFPNPVRTVF	162 SRQVLEGHV
138 SEHWKVQRRA	198 VVAVANVMSA	161 RSRQVLEGH
124 RVVSGGRSMA	164 QVLEGHVLSE	153 RNFFTRQPR
110 QGSAFADRPA	114 FADRPAFASF	145 RRAAHSMMR
104 HQALVQQGSA	102 AIHQALVQQG	128 GGRSMAFGH
97 LNGERAIHQA	38 RLLRQRRRQL	127 SGGRSMAFG
93 PIVVLNGERA	481 FLFISILAHQ	122 SFRVVSGGR
69 AAHLSFARLA	421 FVNQWSVNHD	121 ASFRVVSGG
66 VGQAAHLSFA	385 LYEAMRFSSF	105 QALVQQGSA
60 IGNAAAVGQA	359 ELDQVVGRDR	104 HQALVQQGS
54 PFAWPLIGNA	334 TLSTALQWLL	97 LNGERAIHQ
47 LRSAPPGPFA	287 AAPRDMMDAF	92 CPIVVLNGE
41 RQRRRQLRSA	271 FILDKFLRHC	91 SCPIVVLNG
22 TLLLLLSVLA	165 VLEGHVLSEA	86 QIRLGSCPI
530 DSAVQNLQAK	146 RAAHSMMRNF	80 RYGDVFQIR
524 ESMELLDSAV	128 GGRSMAFGHY	76 RLARRYGDV
493 FRANPNEPAK	34 HVGQRLLRQR	75 ARLARRYGD
487 LAHQCDFRAN	15 PLSIQQTTLL	65 AVGQAAHLS
480 LFLFISILAH	12 PLNPLSIQQT	56 AWPLIGNAA

435 PNPENFDPAR
397 VTIPHATTAN
394 FVPVTIPHAT
380 YVLAFLYEAM
375 QPNLPYVLAF
350 PDVQTRVQAE
330 ASQDTLSTAL
322 ATITDIFGAS
314 RLDLENVPAT
305 AGDSHGGGAR
292 MMDAFILSAE
287 AAPRDMMDAF
229 EEFGRTVGAG

199 VAVANVMSAV
194 RPLTVVAVAN
192 DPRPLTVVAV
181 LVRGSADGAF

178 VALLVRGSAD

171 LSEARELVAL
166 LEGHVLSEAR
125 VVSGGRSMAF
113 AFADRPAFAS
111 GSAFADRPAF
107 LVQQGSAFAD
105 QALVQQGSAF
98 NGERAIHQAL
94 IVVLNGERAI
70 AHLSFARLAR
67 GQAAHLSFAR
48 RSAPPGPFAW
42 QRRRQLRSAP
23 LLLLLSVLAT
531 SAVQNLQAKE
525 SMELLDSAVQ
494 RANPNEPAKM
488 AHQCDFRANP
481 FLFISILAHQ
436 NPENFDPARF
398 TIPHATTANT
395 VPVTIPHATT
381 VLAFLYEAMR
376 PNLPYVLAFL
351 DVQTRVQAEL
331 SQDTLSTALQ
323 TITDIFGASQ
315 LDLENVPATI
306 GDSHGGGARL
298 LSAEKKAAGD
293 MDAFILSAEK
288 APRDMMDAFI
281 ESLRPGAAPR

230 EFGRTVGAGS

200 AVANVMSAVC
195 PLTVVAVANV

473 EELSKMQLFL
472 GEELSKMQLF
459 RVMIFSVGKR
456 LTSRVMIFSV
454 KDLTSRVMIF
450 GLINKDLTSR
445 FLDKDGLINK
412 YHIPKDTVVF
397 VTIPHATTAN
376 PNLPYVLAFL
375 QPNLPYVLAF
346 FTRYPDVQTR
340 QWLLLLFTRY

337 TALQWLLLLF
314 RLDLENVPAT
259 REFEQLNRNF
252 NPVRTVFREF

241 VDVMPWLQYF

235 VGAGSLVDVM
234 TVGAGSLVDV
229 EEFGRTVGAG
223 ELLSHNEEFG
220 EFRELLSHNE
215 SHDDPEFREL
190 FLDPRPLTVV
187 DGAFLDPRPL
68 QAAHLSFARL
20 QTTLLLLLSV
7 PNDPWPLNPL
509 LTIKPKSFKV
496 NPNEPAKMNF
461 MIFSVGKRRC
426 SVNHDPLKWP
406 NTSVLGYHIP
393 SFVPVTIPHA
382 LAFLYEAMRF
316 DLENVPATIT
230 EFGRTVGAGS
195 PLTVVAVANV
192 DPRPLTVVAV
172 SEARELVALL
171 LSEARELVAL
119 AFASFRVVSG
71 HLSFARLARR
29 VLATVHVGQR
530 DSAVQNLQAK
499 EPAKMNFSYG
478 MQLFLFISIL
470 CIGEELSKMQ
451 LINKDLTSRV
439 NFDPARFLDK

419 VVFVNQWSVN

398 TIPHATTANT
343 LLLFTRYPDV

52 PGPFAWPLI
45 RQLRSAPPG
40 LRQRRRQLR
25 LLLSVLATV
21 TTLLLLLSV
14 NPLSIQQTT
13 LNPLSIQQT
11 WPLNPLSIQ
1 MGTSLSPND

182 VRGSADGAFL
179 ALLVRGSADG
172 SEARELVALL
167 EGHVLSEARE

141 WKVQRRAAHS
126 VSGGRSMAFG
114 FADRPAFASF

108 VQQGSAFADR
99 GERAIHQALV
95 VVLNGERAIH
71 HLSFARLARR
68 QAAHLSFARL

63 AAAVGQAAHL
58 PLIGNAAAVG
49 SAPPGPFAWP
43 RRRQLRSAPP
24 LLLLSVLATV

HLA-A*0203 Octamers

Pos 12345678
531 SAVQNLQA
525 SMELLDSA
494 RANPNEPA
488 AHQCDFRA
481 FLFISILA
436 NPENFDPA
398 TIPHATTA
395 VPVTIPHA
381 VLAFLYEA
376 PNLPYVLA

351 DVQTRVQA

331 SQDTLSTA
323 TITDIFGA
315 LDLENVPA
306 GDSHGGGA

298 LSAEKKAA
297 ILSAEKKA
293 MDAFILSA
288 APRDMMDA
281 ESLRPGAA
280 CESLRPGA
230 EFGRTVGA
200 AVANVMSA
195 PLTVVAVA

193 PRPLTVVA
182 VRGSADGA
179 ALLVRGSA
172 SEARELVA
167 EGHVLSEA
141 WKVQRRAA

324 ITDIFGASQD
323 TITDIFGASQ
270 NFILDKFLRH
260 EFEQLNRNFS

256 TVFREFEQLN
238 GSLVDVMPWL
212 CRYSHDDPEF

124 RVVSGGRSMA
111 GSAFADRPAF
72 LSFARLARRY
58 PLIGNAAAVG
24 LLLLSVLATV

23 LLLLLSVLAT
498 NEPAKMNFSY
494 RANPNEPAKM
492 DFRANPNEPA
484 ISILAHQCDF
471 IGEELSKMQL

464 SVGKRRCIGE
436 NPENFDPARF
394 FVPVTIPHAT
374 DQPNLPYVLA
362 QVVGRDRLPC
338 ALQWLLLLFT
318 ENVPATITDI
296 FILSAEKKAA
291 DMMDAFILSA
282 SLRPGAAPRD
233 RTVGAGSLVD
205 MSAVCFGCRY
203 NVMSAVCFGC

200 AVANVMSAVC

197 TVVAVANVMS
177 LVALLVRGSA
156 FTRQPRSRQV
107 LVQQGSAFAD

105 QALVQQGSAF
59 LIGNAAAVGQ
54 PFAWPLIGNA
28 SVLATVHVGQ
18 IQQTTLLLLL
532 AVQNLQAKET
507 YGLTIKPKSF
483 FISILAHQCD
480 LFLFISILAH

418 TVVFVNQWSV
402 ATTANTSVLG
384 FLYEAMRFSS
381 VLAFLYEAMR
371 CMGDQPNLPY
355 RVQAELDQVV

140 HWKVQRRA	283 LRPGAAPRDM
126 VSGGRSMA	222 RELLSHNEEF
114 FADRPAFA	218 DPEFRELLSH
112 SAFADRPA	216 HDDPEFRELL
108 VQQGSAFA	207 AVCFGCRYSH
106 ALVQQGSA	201 VANVMSAVCF
99 GERAIHQA	169 HVLSEARELV
95 VVLNGERA	157 TRQPRSRQVL
71 HLSFARLA	147 AAHSMMRNFF
68 QAAHLSFA	96 VLNGERAIHQ
63 AAAVGQAA	95 VVLNGERAIH
62 NAAAVGQA	94 IVVLNGERAI
58 PLIGNAAA	93 PIVVLNGERA
57 WPLIGNAA	86 QIRLGSCPIV
56 AWPLIGNA	63 AAAVGQAAHL
49 SAPPGPFA	50 APPGPFAWPL
43 RRRQLRSA	16 LSIQQTTLLL
24 LLLLSVLA	528 LLDSAVQNLQ
	524 ESMELLDSAV
	521 TLRESMELLD
	500 PAKMNFSYGL
	486 ILAHQCDFRA
	485 SILAHQCDFR
	482 LFISILAHQC
	479 QLFLFISILA
	452 INKDLTSRVM
	396 PVTIPHATTA
	383 AFLYEAMRFS
	373 GDQPNLPYVL
	369 LPCMGDQPNL
	368 RLPCMGDQPN
	353 QTRVQAELDQ
	344 LLFTRYPDVQ
	330 ASQDTLSTAL
	308 SHGGGARLDL
	306 GDSHGGGARL
	297 ILSAEKKAAG
	272 ILDKFLRHCE
	253 PVRTVFREFE
	208 VCFGCRYSHD
	182 VRGSADGAFL
	170 VLSEARELVA
	143 VQRRAAHSMM
	106 ALVQQGSAFA
	98 NGERAIHQAL
	80 RYGDVFQIRL
	39 LLRQRRRQLR
	32 TVHVGQRLLR
	30 LATVHVGQRL
	26 LLSVLATVHV
	2 GTSLSPNDPW
	513 PKSFKVNVTL
	508 GLTIKPKSFK
	466 GKRRCIGEEL
	442 PARFLDKDGL

438 ENFDPARFLD
430 DPLKWPNPEN
423 NQWSVNHDPL
401 HATTANTSVL
367 DRLPCMGDQP
360 LDQVVGRDRL
301 EKKAAGDSHG
295 AFILSAEKKA
294 DAFILSAEKK
289 PRDMMDAFIL
284 RPGAAPRDMM
276 FLRHCESLRP
257 VFREFEQLNR
246 WLQYFPNPVR
239 SLVDVMPWLQ
231 FGRTVGAGSL
224 LLSHNEEFGR
217 DDPEFRELLS
180 LLVRGSADGA
179 ALLVRGSADG
168 GHVLSEAREL
154 NFFTRQPRSR
123 FRVVSGGRSM
113 AFADRPAFAS
25 LLLSVLATVH
22 TLLLLLSVLA
14 NPLSIQQTTL
9 DPWPLNPLSI
515 SFKVNVTLRE
437 PENFDPARFL

420 VFVNQWSVNH
409 VLGYHIPKDT
390 RFSSFVPVTI
389 MRFSSFVPVT
345 LFTRYPDVQT
342 LLLLFTRYPD
341 WLLLLFTRYP
335 LSTALQWLLL
307 DSHGGGARLD

286 GAAPRDMMDA
268 FSNFILDKFL
264 LNRNFSNFIL
263 QLNRNFSNFI
248 QYFPNPVRTV
219 PEFRELLSHN
173 EARELVALLV
167 EGHVLSEARE
162 SRQVLEGHVL
155 FFTRQPRSRQ

139 EHWKVQRRAA
116 DRPAFASFRV
101 RAIHQALVQQ
49 SAPPGPFAWP
514 KSFKVNVTLR
504 NFSYGLTIKP
503 MNFSYGLTIK

446 LDKDGLINKD
444 RFLDKDGLIN
441 DPARFLDKDG
415 PKDTVVFVNQ
372 MGDQPNLPYV
350 PDVQTRVQAE
292 MMDAFILSAE
281 ESLRPGAAPR
275 KFLRHCESLR
266 RNFSNFILDK
189 AFLDPRPLTV
185 SADGAFLDPR
145 RRAAHSMMRN
131 SMAFGHYSEH

126 VSGGRSMAFG
122 SFRVVSGGRS

108 VQQGSAFADR
100 ERAIHQALVQ
97 LNGERAIHQA
90 GSCPIVVLNG
84 VFQIRLGSCP
79 RRYGDVFQIR
73 SFARLARRYG
53 GPFAWPLIGN
33 VHVGQRLLRQ
512 KPKSFKVNVT
505 FSYGLTIKPK
497 PNEPAKMNFS
487 LAHQCDFRAN
465 VGKRRCIGEE
462 IFSVGKRRCI
449 DGLINKDLTS
440 FDPARFLDKD
434 WPNPENFDPA
414 IPKDTVVFVN
387 EAMRFSSFVP
361 DQVVGRDRLP
358 AELDQVVGRD
357 QAELDQVVGR
354 TRVQAELDQV
329 GASQDTLSTA
327 IFGASQDTLS
311 GGARLDLENV
309 HGGGARLDLE
251 PNPVRTVFRE
244 MPWLQYFPNP
209 CFGCRYSHDD

199 VAVANVMSAV
193 PRPLTVVAVA
184 GSADGAFLDP
175 RELVALLVRG
159 QPRSRQVLEG

137 YSEHWKVQRR
133 AFGHYSEHWK
120 FASFRVVSGG

91	SCPIVVLNGE
10	PWPLNPLSIQ
523	RESMELLDSA
522	LRESMELLDS
516	FKVNVTLRES
477	KMQLFLFISI
476	SKMQLFLFIS
475	LSKMQLFLFI
457	TSRVMIFSVG
435	PNPENFDPAR
428	NHDPLKWPNP
416	KDTVVFVNQW
388	AMRFSSFVPV
379	PYVLAFLYEA
321	PATITDIFGA
298	LSAEKKAAGD
258	FREFEQLNRN
243	VMPWLQYFPN
237	AGSLVDVMPW
225	LSHNEEFGRT
160	PRSRQVLEGH
150	SMMRNFFTRQ
132	MAFGHYSEHW
117	RPAFASFRVV
89	LGSCPIVVLN
81	YGDVFQIRLG
78	ARRYGDVFQI
66	VGQAAHLSFA
60	IGNAAAVGQA
41	RQRRRQLRSA
511	IKPKSFKVNV
501	AKMNFSYGLT
404	TANTSVLGYH
391	FSSFVPVTIP
378	LPYVLAFLYE
366	RDRLPCMGDQ
356	VQAELDQVVG
339	LQWLLLLFTR
303	KAAGDSHGGG
290	RDMMDAFILS
278	RHCESLRPGA
277	LRHCESLRPG
265	NRNFSNFILD
204	VMSAVCFGCR
202	ANVMSAVCFG
174	ARELVALLVR
153	RNFFTRQPRS
149	HSMMRNFFTR
136	HYSEHWKVQR
75	ARLARRYGDV
48	RSAPPGPFAW
27	LSVLATVHVG

19	QQTTLLLLLS
531	SAVQNLQAKE
493	FRANPNEPAK
491	CDFRANPNEP
490	QCDFRANPNE
460	VMIFSVGKRR
453	NKDLTSRVMI
365	GRDRLPCMGD
349	YPDVQTRVQA
347	TRYPDVQTRV
328	FGASQDTLST
325	TDIFGASQDT
315	LDLENVPATI
305	AGDSHGGGAR
300	AEKKAAGDSH
293	MDAFILSAEK
285	PGAAPRDMMD
250	FPNPVRTVFR
236	GAGSLVDVMP
188	GAFLDPRPLT
141	WKVQRRAAHS
140	HWKVQRRAAH
121	ASFRVVSGGR
118	PAFASFRVVS
115	ADRPAFASFR
112	SAFADRPAFA
92	CPIVVLNGER
62	NAAAVGQAAH
61	GNAAAVGQAA
56	AWPLIGNAAA
55	FAWPLIGNAA
51	PPGPFAWPLI
526	MELLDSAVQN
518	VNVTLRESME
506	SYGLTIKPKS
495	ANPNEPAKMN
488	AHQCDFRANP
463	FSVGKRRCIG
458	SRVMIFSVGK
443	ARFLDKDGLI
432	LKWPNPENFD
405	ANTSVLGYHI
400	PHATTANTSV
392	SSFVPVTIPH
386	YEAMRFSSFV
370	PCMGDQPNLP
364	VGRDRLPCMG
348	RYPDVQTRVQ
331	SQDTLSTALQ
313	ARLDLENVPA
304	AAGDSHGGGA
302	KKAAGDSHGG

288	APRDMMDAFI
280	CESLRPGAAP
279	HCESLRPGAA
273	LDKFLRHCES
269	SNFILDKFLR
247	LQYFPNPVRT
228	NEEFGRTVGA
227	HNEEFGRTVG
226	SHNEEFGRTV
214	YSHDDPEFRE
194	RPLTVVAVAN
191	LDPRPLTVVA
186	ADGAFLDPRP
178	VALLVRGSAD
161	RSRQVLEGHV
158	RQPRSRQVLE
144	QRRAAHSMMR
109	QQGSAFADRP
104	HQALVQQGSA
103	IHQALVQQGS
87	IRLGSCPIVV
85	FQIRLGSCPI
70	AHLSFARLAR
67	GQAAHLSFAR
64	AAVGQAAHLS
57	WPLIGNAAAV
45	RQLRSAPPGP
43	RRRQLRSAPP
42	QRRRQLRSAP
35	VGQRLLRQRR
13	LNPLSIQQTT
8	NDPWPLNPLS
6	SPNDPWPLNP
5	LSPNDPWPLN
3	TSLSPNDPWP
534	QNLQAKETCQ
529	LDSAVQNLQA
525	SMELLDSAVQ
489	HQCDFRANPN
468	RRCIGEELSK
433	KWPNPENFDP
429	HDPLKWPNPE
427	VNHDPLKWPN
425	WSVNHDPLKW
424	QWSVNHDPLK
395	VPVTIPHATT
332	QDTLSTALQW
320	VPATITDIFG
310	GGGARLDLEN
299	SAEKKAAGDS
261	FEQLNRNFSN
254	VRTVFREFEQ
245	PWLQYFPNPV
232	GRTVGAGSLV
221	FRELLSHNEE

166	LEGHVLSEAR
163	RQVLEGHVLS
152	MRNFFTRQPR
151	MMRNFFTRQP
138	SEHWKVQRRA
135	GHYSEHWKVQ
134	FGHYSEHWKV
130	RSMAFGHYSE
127	SGGRSMAFGH
99	GERAIHQALV
82	GDVFQIRLGS
77	LARRYGDVFQ
74	FARLARRYGD
52	PGPFAWPLIG
47	LRSAPPGPFA
44	RRQLRSAPPG
40	LRQRRRQLRS
37	QRLLRQRRRQ
36	GQRLLRQRRR
11	WPLNPLSIQQ
1	MGTSLSPNDP

Prediction of HLA binding peptides from cytochrome P450 1B1 using the algorithm on the BIMAS website (http://bimas.dcrt.nih.gov/molbio/hla_bind/)

HLA-allele	peptide length	rank	starting position in the protein	sequence	score
A1	9mer	1	372	MGDQPNLPY	31.25
		2	137	YSEHWKVQR	27
	10mer	1	240	LVDVmPWLQY	125
		2	439	NFDPaRFLDK	25
A_1101	9mer	1	459	RVMIFSVGK	12
		2	408	SVLGYHIPK	6
	10mer	1	459	RVMIfSVGKR	2.4
		2	508	GLTIkPKSFK	1.2
A_0201	9mer	1	246	WLQYFPNPV	1215.769
		2	239	SLVDVMPWL	1107.961
	10mer	1	24	LLLLsVLATV	1006.209
		2	343	LLLFtRYPDV	656.223
A_0205	9mer	1	479	QLFLFISIL	84
		2	239	SLVDVMPWL	42
	10mer	1	478	MQLFIFISIL	114.24
		2	24	LLLLsVLATV	20.4
A3	9mer	1	150	SMMRNFFTR	54
		2	408	SVLGYHIPK	27
	10mer	1	508	GLTIkPKSFK	90
		2	445	FLDKdGLINK	60
A_3101	9mer	1	150	SMMRNFFTR	36
		2	460	VMIFSVGKR	8
	10mer	1	459	RVMIfSVGKR	36
		2	339	LQWLILLFTR	36
A_3302	9mer	1	72	LSFARLARR	15
		2	225	LSHNEEFGR	15
	10mer	1	281	ESLRpGAAPR	45
		2	359	ELDQvVGRDR	27
A24	9mer	1	213	RYSHDDPEF	220
		2	275	KFLRHCESL	60
	10mer	1	80	RYGDvFQIRL	480
		2	385	LYEAmRFSSF	180
A68.1	9mer	1	408	SVLGYHIPK	240
		2	459	RVMIFSVGK	240
	10mer	1	459	RVMIfSVGKR	400
		2	34	HVGQrLLRQR	400
B7	9mer	1	173	EARELVALL	120
		2	39	LLRQRRRQL	60
	10mer	1	50	APPGpFAWPL	240
		2	288	APRDmMDAFI	240
B8	9mer	1	39	LLRQRRRQL	160

		2	173	EARELVALL	48
	10mer	1	156	FTRQpRSRQV	12
		2	512	KPKSfKVNVT	8
B14	9mer	1	443	ARFLDKDGL	100
		2	361	DQVVGRDRL	45
	10mer	1	38	RLLRqRRRQL	250
		2	75	ARLArRYGDV	200
B_2702	9mer	1	79	RRYGDVFQI	900
		2	443	ARFLDKDGL	300
	10mer	1	212	CRYShDDPEF	1000
		2	443	ARFLdKDGLI	300
B_2705	9mer	1	443	ARFLDKDGL	10000
		2	79	RRYGDVFQI	9000
	10mer	1	79	RRYGdVFQIR	15000
		2	468	RRCIgEELSK	6000
B40	9mer	1	229	EEFGRTVGA	80
		2	172	SEARELVAL	40
	10mer	1	473	EELSkMQLFL	40
		2	172	SEAReLVALL	40
B60	9mer	1	172	SEARELVAL	640
		2	472	GEELSKMQL	352
	10mer	1	473	EELSkMQLFL	640
		2	172	SEAReLVALL	352
B61	9mer	1	229	EEFGRTVGA	60
		2	280	CESLRPGAA	20
	10mer	1	46	QLRSaPPGPF	120
		2	377	NLPYvLAFLY	80
B62	9mer	1	338	ALQWLLLLF	96
		2	341	WLLLLFTRY	96
	10mer	1	46	QLRSaPPGPF	120
		2	377	NLPYvLAFLY	80
B_3501	9mer	1	288	APRDMMDAF	120
		2	284	RPGAAPRDM	80
	10mer	1	284	RPGAaPRDMM	80
		2	288	APRDmMDAFI	48
B_3701	9mer	1	217	DDPEFRELL	200
		2	454	KDLTSRVMI	200
	10mer	1	148	AHSMMRNFF	39
		2	428	NHDPLKWPN	11.7
B_3801	9mer	1	148	AHSMMRNFF	39
		2	428	NHDPLKWPN	11.7
	10mer	1	148	AHSMMRNFF	39
		2	428	NHDPLKWPN	11.7
B_3901	9mer	1	135	GHYSEHWKV	60
		2	412	YHIPKDTVV	30
	10mer	1	215	SHDDpEFREL	540
		2	168	GHVLsEAREL	180
B_3902	9mer	1	19	QQTTLLLLL	24

		2	374	DQPNLPYVL	24
	10mer	1	447	DKDGIINKDL	24
		2	478	MQLFIFISIL	24
B_4403	9mer	1	473	EELSKMQLF	120
		2	386	YEAMRFSSF	80
	10mer	1	498	NEPAkMNFSY	180
		2	222	RELLsHNEEF	80
B_5101	9mer	1	414	IPKDTVVFV	314.6
		2	387	EAMRFSSFV	200
	10mer	1	9	DPWPINPLSI	1600
		2	288	APRDmMDAFI	440
B_5102	9mer	1	117	RPAFASFRV	400
		2	188	GAFLDPRPL	302.5
	10mer	1	9	DPWPINPLSI	2200
		2	57	WPLIgNAAAV	660
B_5103	9mer	1	401	HATTANTSV	121
		2	387	EAMRFSSFV	110
	10mer	1	410	LGYHiPKDTV	132
		2	199	VAVAnVMSAV	121
B_5201	9mer	1	356	VQAELDQVV	396
		2	374	DQPNLPYVL	88
	10mer	1	478	MQLFIFISIL	90
		2	117	RPAFaSFRVV	50
B_5801	9mer	1	238	GSLVDVMPW	105.6
		2	49	SAPPGPFAW	80
	10mer	1	48	RSAPpGPFAW	480
		2	146	RAAHsMMRNF	99

CLAIMS

1. A method of treating a patient that comprises or is at risk of comprising a cell that expresses cytochrome P450 1B1, said method comprising administering to said patient a cytotoxic T lymphocyte that kills said cell in a cytochrome P450 1B1-specific, major histocompatibility complex-restricted fashion.

2. The method of claim 1, wherein said cytotoxic T lymphocyte is autologous to said patient.

3. The method of claim 1, wherein said cytotoxic T lymphocyte is allogeneic to said patient.

4. The method of claim 1, wherein said cytotoxic T lymphocyte is generated by activation with an antigen presenting cell that has been pulsed with cytochrome P450 1B1 or a peptide of cytochrome P450 1B1 that binds to a major histocompatibility complex molecule.

5. The method of claim 1, further comprising administering to said patient a cytotoxic T lymphocyte that kills a cell in said patient that expresses a second tumor associated antigen.

6. The method of claim 5, wherein said second tumor associated antigen is telomerase.

7. A method of treating a patient that comprises or is at risk of comprising a cell that expresses cytochrome P450 1B1, said method comprising administering to said patient an antigen presenting cell that activates in said patient a cytotoxic T lymphocyte that kills said cell in a cytochrome P450 1B1-specific, major histocompatibility complex-restricted fashion.

8. The method of claim 7, wherein said antigen presenting cell has been pulsed with cytochrome P450 1B1 or a peptide of cytochrome P450 1B1 that binds to a major histocompatibility complex molecule.

9. The method of claim 7, further comprising administering to said patient an antigen presenting cell that activates in said patient a cytotoxic T lymphocyte that kills a cell in said patient that expresses a second tumor associated antigen.

10. The method of claim 9, wherein said second tumor associated antigen is telomerase.

11. A method of treating a patient that comprises or is at risk of comprising a cell that expresses cytochrome P450 1B1, said method comprising administering to said patient a peptide of cytochrome P450 1B1 that binds to a major histocompatibility complex molecule, wherein said peptide of cytochrome P450 1B1 is processed by an antigen presenting cell in said patient, which activates a cytotoxic T lymphocyte in said patient to kill said cell that expresses cytochrome P450 1B1 in a cytochrome P450 1B1-specific, major histocompatibility complex-restricted fashion.

12. The method of claim 11, wherein said peptide of cytochrome P450 1B1 is administered to said patient in association with an adjuvant.

13. The method of claim 11, further comprising administering to said patient a second tumor associated antigen or a peptide thereof that binds to a major histocompatibility complex molecule, wherein said second tumor associated antigen or said peptide thereof is processed by an antigen presenting cell in said patient, which activates a cytotoxic T lymphocyte in said patient to kill cells that express the second tumor associated antigen in a tumor associated antigen-specific, major histocompatibility complex-restricted fashion.

14. The method of claim 13, wherein said second tumor associated antigen is telomerase.

15. A method of treating a patient that comprises or is at risk of comprising a cell that expresses cytochrome P450 1B1, said method comprising administering to said patient a nucleic acid molecule encoding cytochrome P450 1B1 or a peptide of cytochrome P450 1B1 that binds to a major histocompatibility complex molecule, wherein said nucleic acid molecule is expressed in said patient so that the polypeptide or peptide it encodes can be processed by an antigen presenting cell in said patient, which activates a cytotoxic T lymphocyte in said patient to kill said cell that expresses cytochrome P450 1B1 in a cytochrome P450 1B1-specific, major histocompatibility complex-restricted fashion.

16. The method of claim 15, wherein said nucleic acid molecule encoding cytochrome P450 1B1 or a peptide of cytochrome P450 1B1 is in an expression vector.

17. The method of claim 15, further comprising administering to said patient a nucleic acid molecule encoding a second tumor associated antigen or a peptide thereof that binds to a major histocompatibility complex molecule, wherein said nucleic acid molecule is expressed in said patient so that the polypeptide or peptide that it encodes can be processed by an antigen presenting cell in said patient, which activates a cytotoxic T lymphocyte in said patient to kill cells that express the second tumor associated antigen in a tumor associated antigen-specific, major histocompatibility complex-restricted fashion.

18. The method of claim 17, wherein the second tumor associated antigen is telomerase.

19. The method of claim 1, 7, 11, or 15, wherein said patient comprises a tumor comprising cells that express cytochrome P450 1B1.

20. The method of claim 4 or 7, wherein said antigen presenting cell is a dendritic cell or a CD40-activated B cell.

21. The method of claim 4, 8, 11, or 15, wherein said peptide of cytochrome P450 1B1 binds to a class I major histocompatibility complex molecule.

22. The method of claim 21, wherein said class I major histocompatibility complex molecule is an HLA-A2 or an HLA-A3 molecule.

23. The method of claim 22, wherein said peptide of cytochrome P450 1B1 comprises the amino acid sequence of CYP239 (SEQ ID NO:1), CYP246 (SEQ ID NO:2), CYP190 (SEQ ID NO:3), or CYP528 (SEQ ID NO:4).

24. A method of assessing the level of immunity of a patient to cytochrome P450 1B1 or a peptide of cytochrome P450 1B1 that binds to a major histocompatibility complex molecule, said method comprising measuring the level of cytotoxic T lymphocytes specific for cytochrome P450 1B1 or said peptide of cytochrome P450 1B1 in a sample from said patient.

25. The method of claim 24, wherein said sample is obtained from said patient before or after a cancer treatment is administered to said patient.

26. A cytochrome P450 1B1 peptide that binds to a major histocompatibility complex molecule.

27. The peptide of claim 26, consisting essentially of the amino acid sequence of CYP239 (SEQ ID NO:1), CYP246 (SEQ ID NO:2), CYP190 (SEQ ID NO:3), or CYP528 (SEQ ID NO:4).

28. An *ex vivo* generated cytotoxic T lymphocyte that specifically kills a cell expressing cytochrome P450 1B1 in a specific, major histocompatibility complex-restricted fashion.

29. An *ex vivo* generated antigen presenting cell that presents a peptide of a cytochrome P450 1B1 in the context of a major histocompatibility complex molecule.

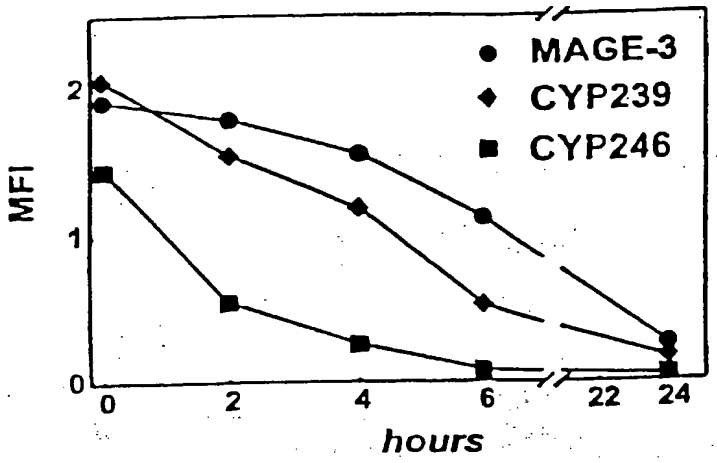
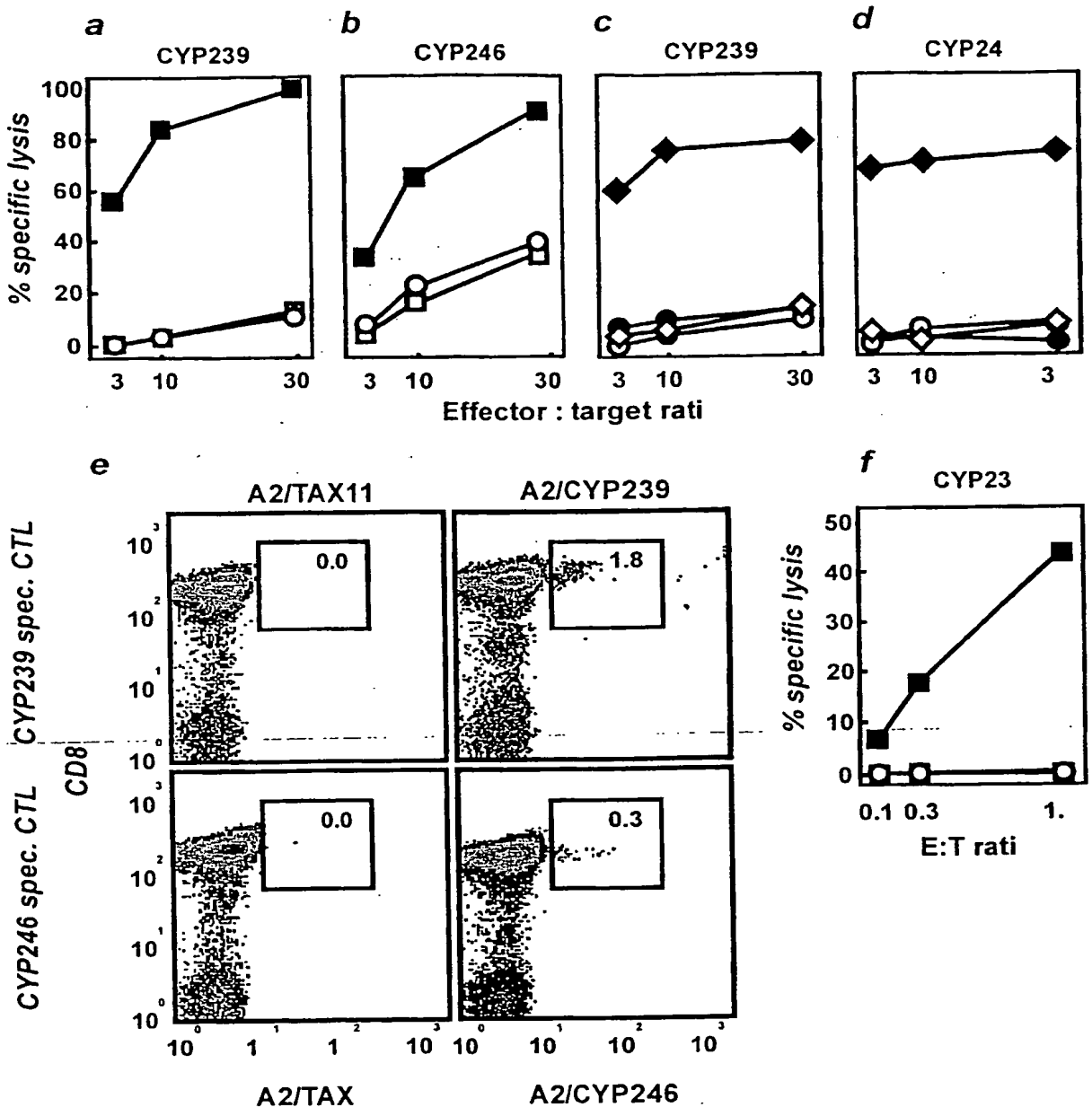


Fig. 1

FIGURE 2



CYP239 SPECIFIC LYSIS OF PULSED CD40-B CELLS IS DEPENDENT ON PEPTIDE CONCENTRATION

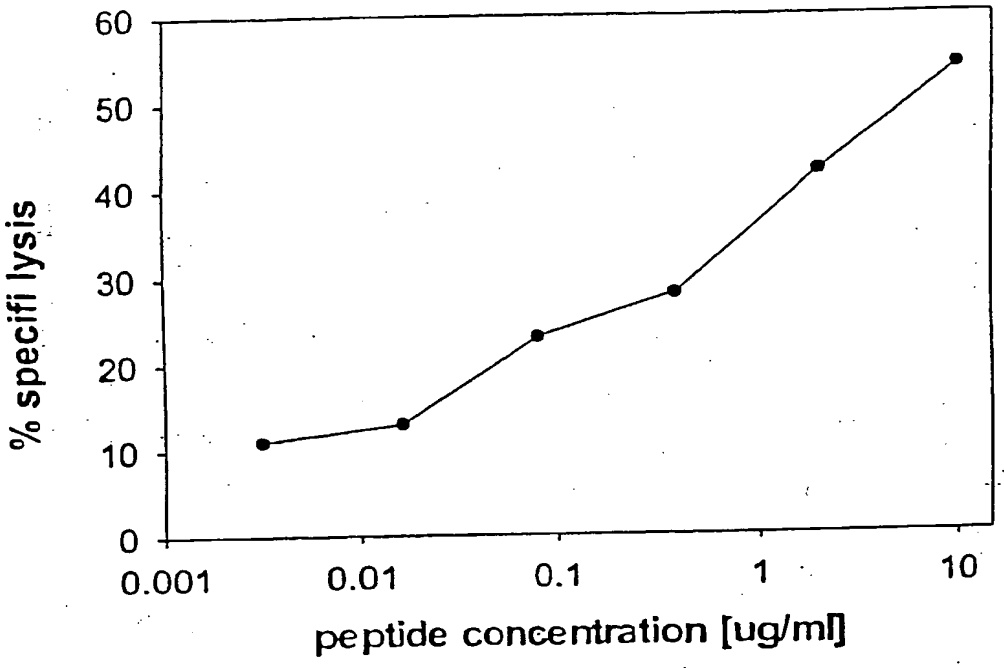
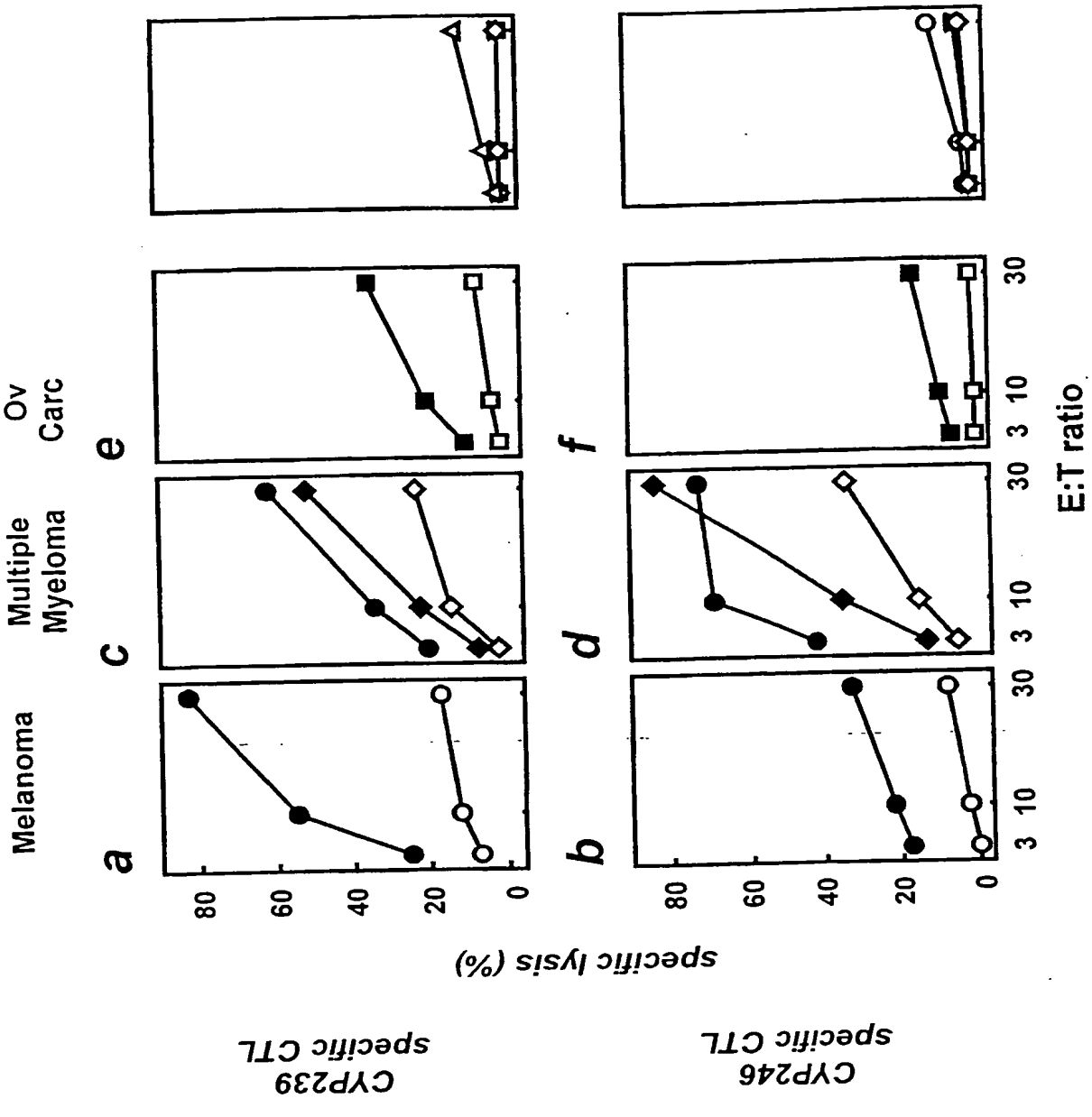


Fig. 3

FIGURE 4



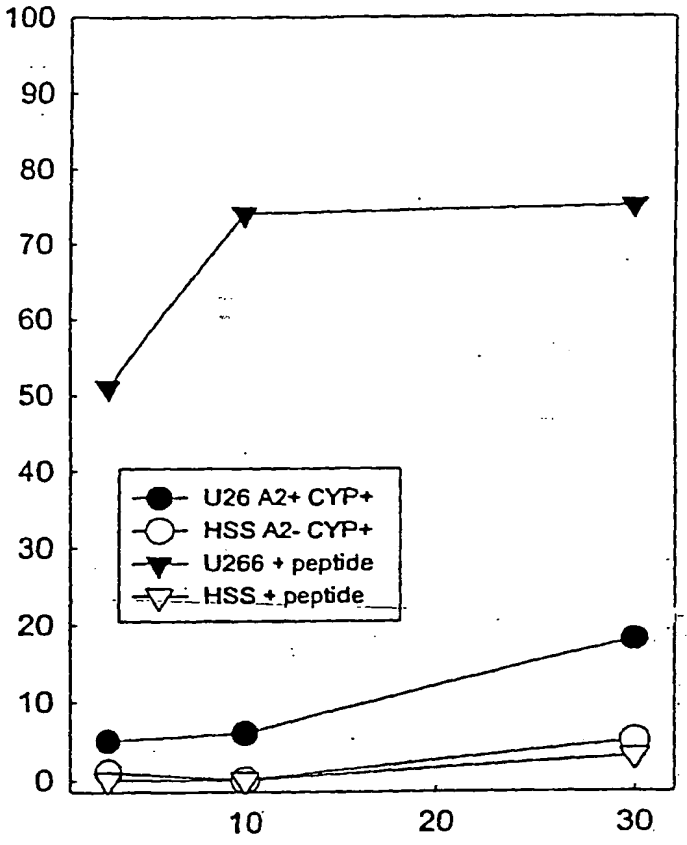
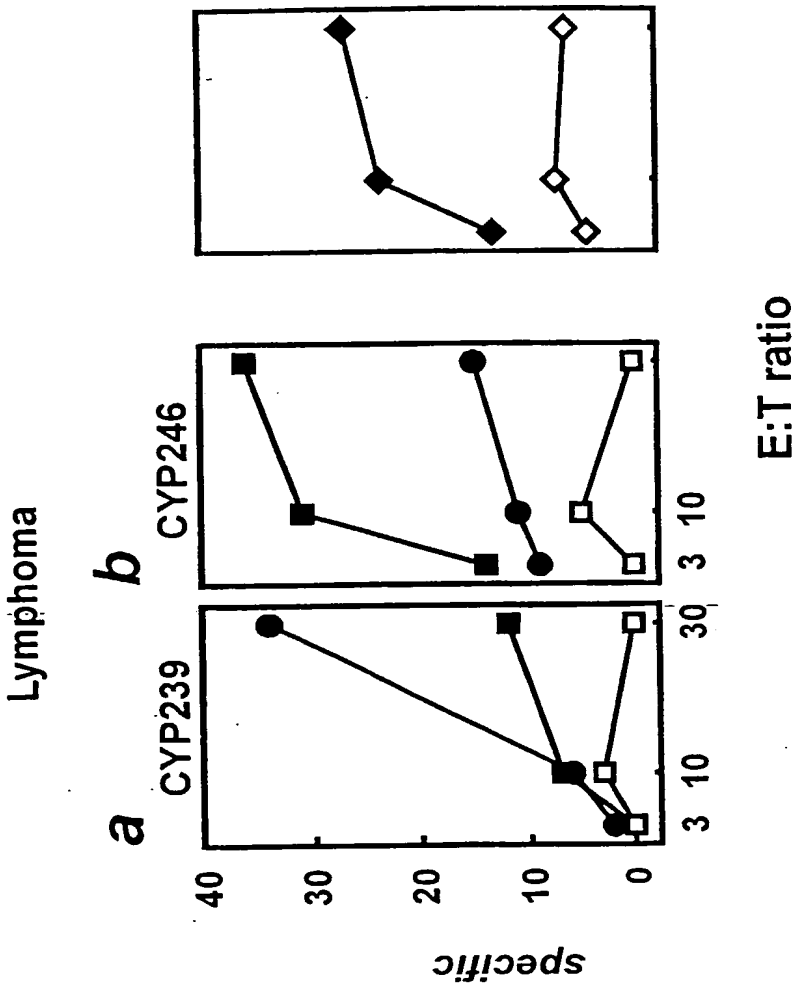


Fig. 5

FIGURE 6



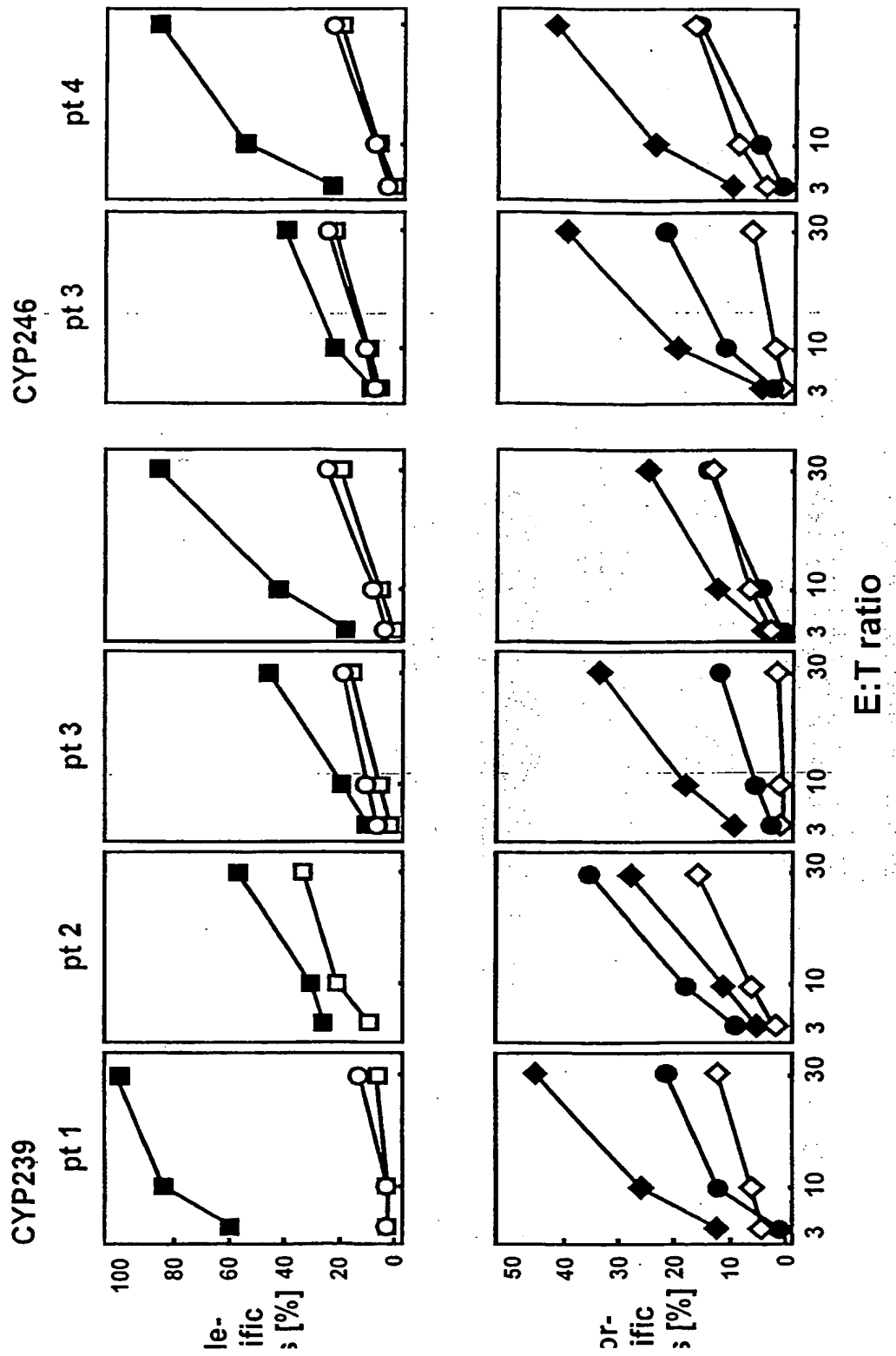
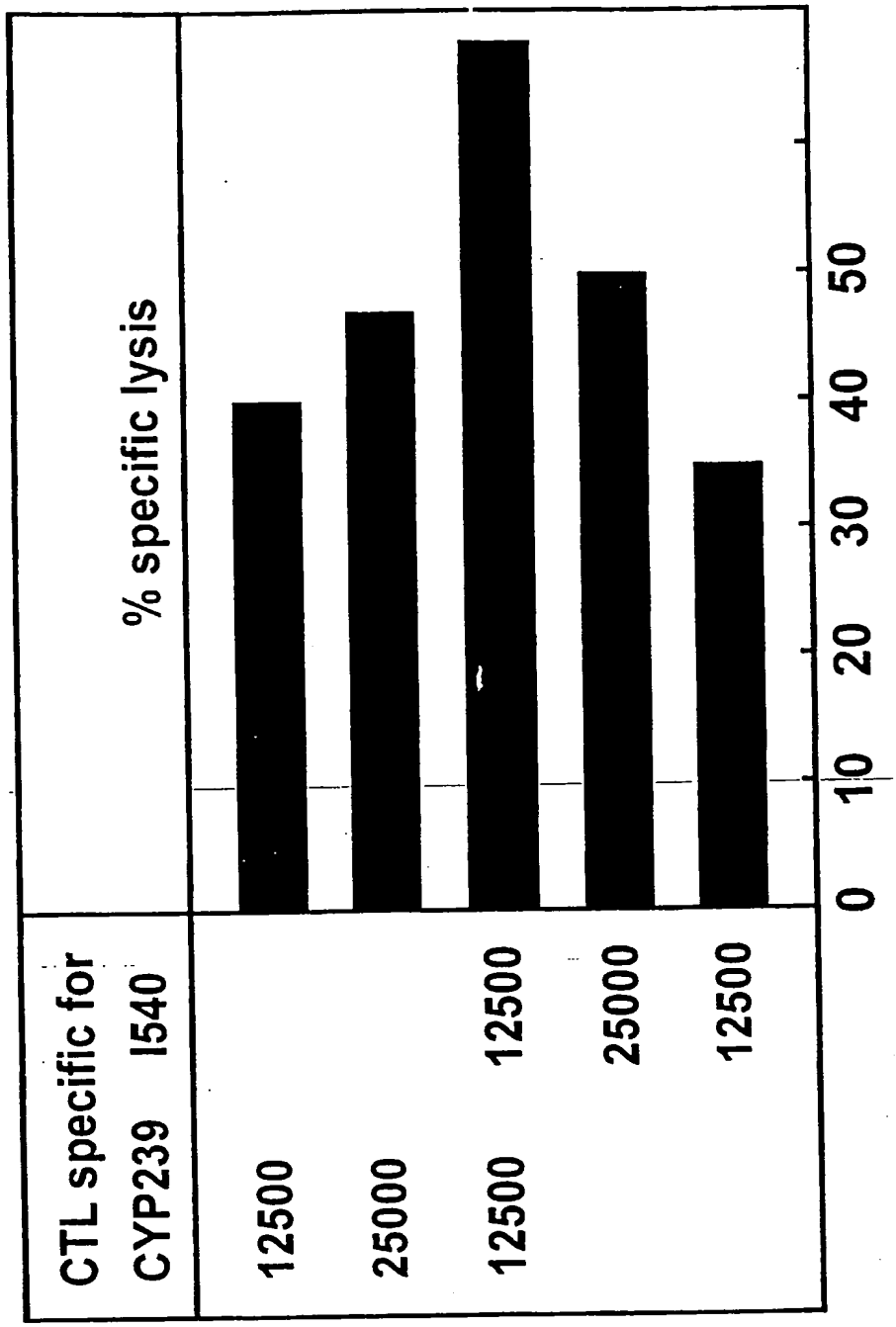


FIGURE 8



Use of heteroclitic peptides

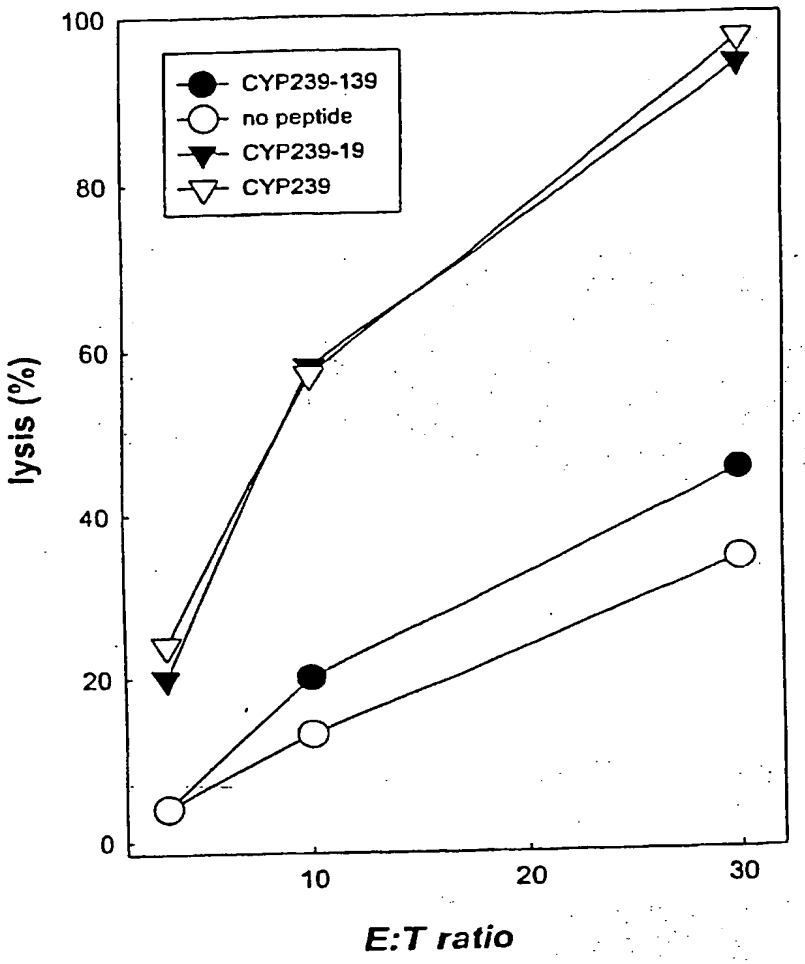


Fig. 9

FIGURE 10

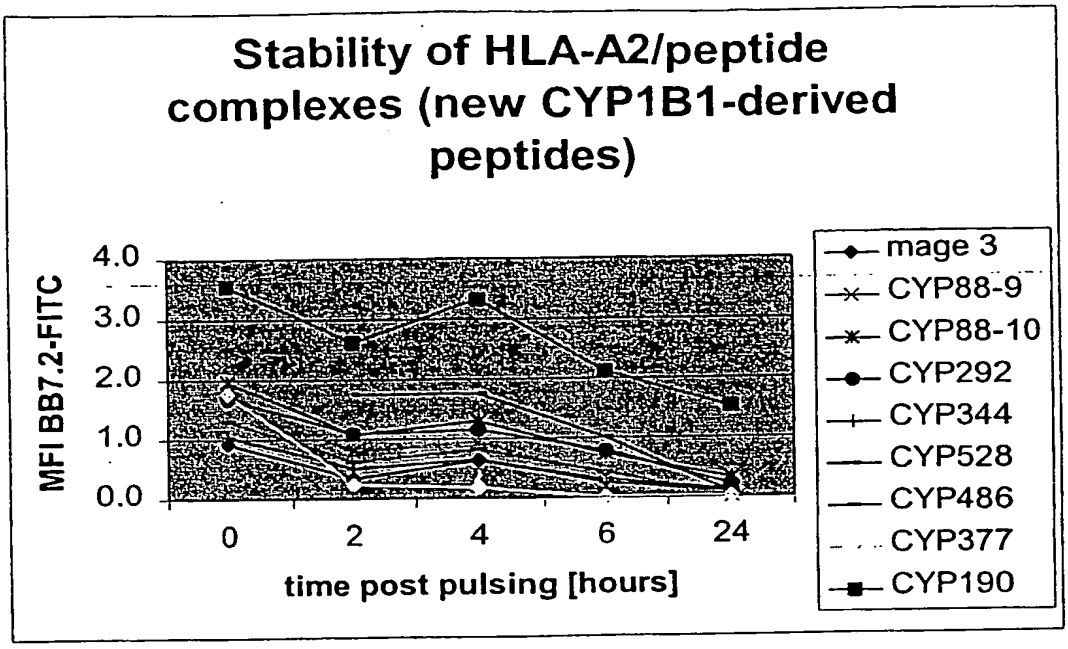


FIGURE 11

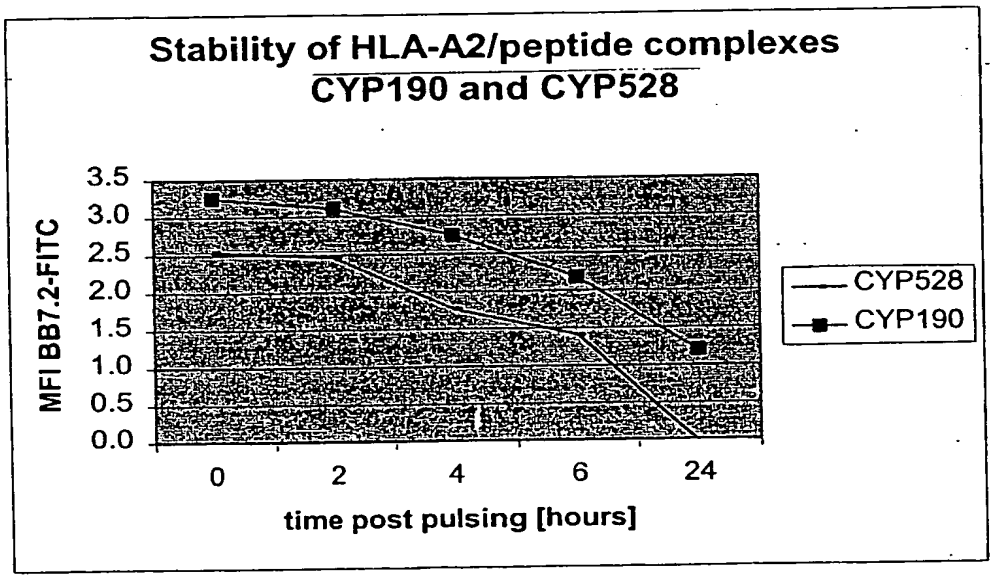


FIGURE 12A

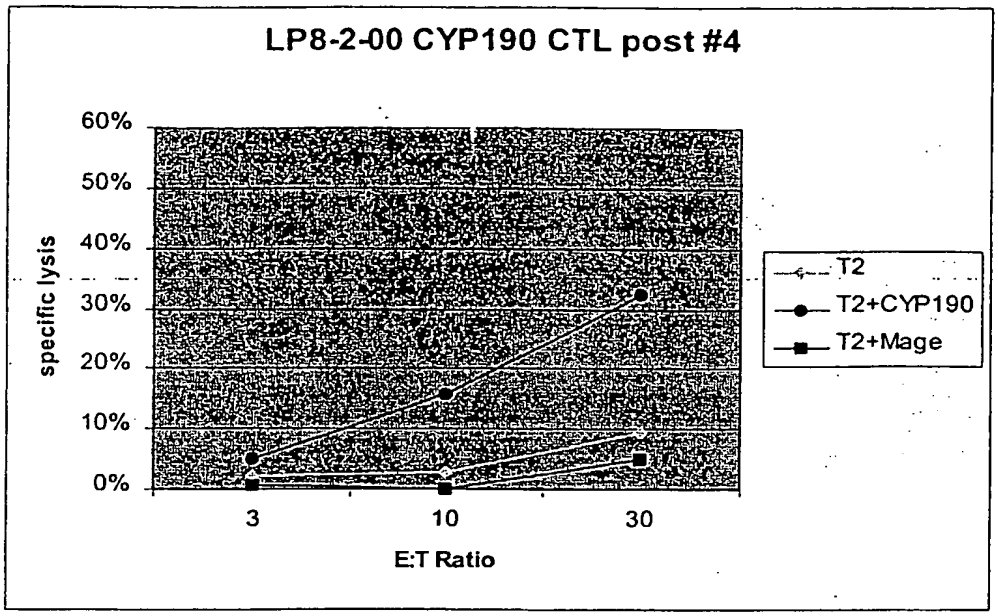


FIGURE 12B

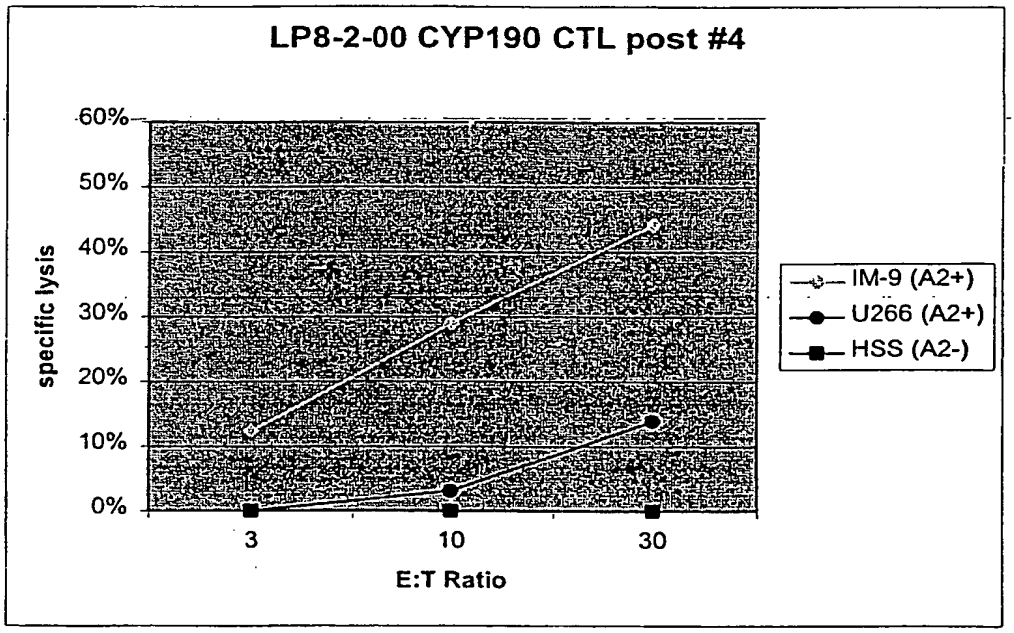


FIGURE 12C

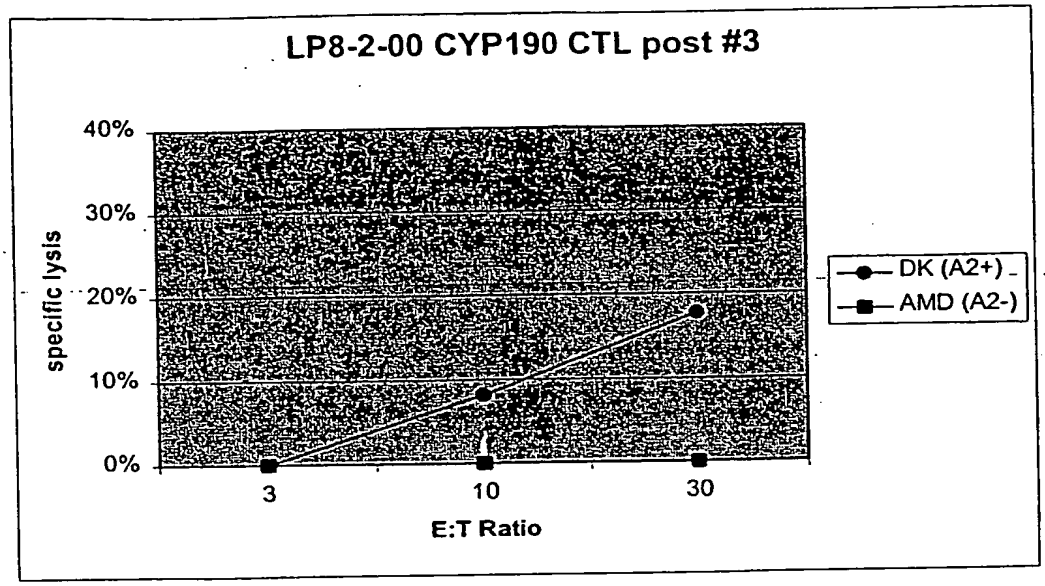


FIGURE 13A

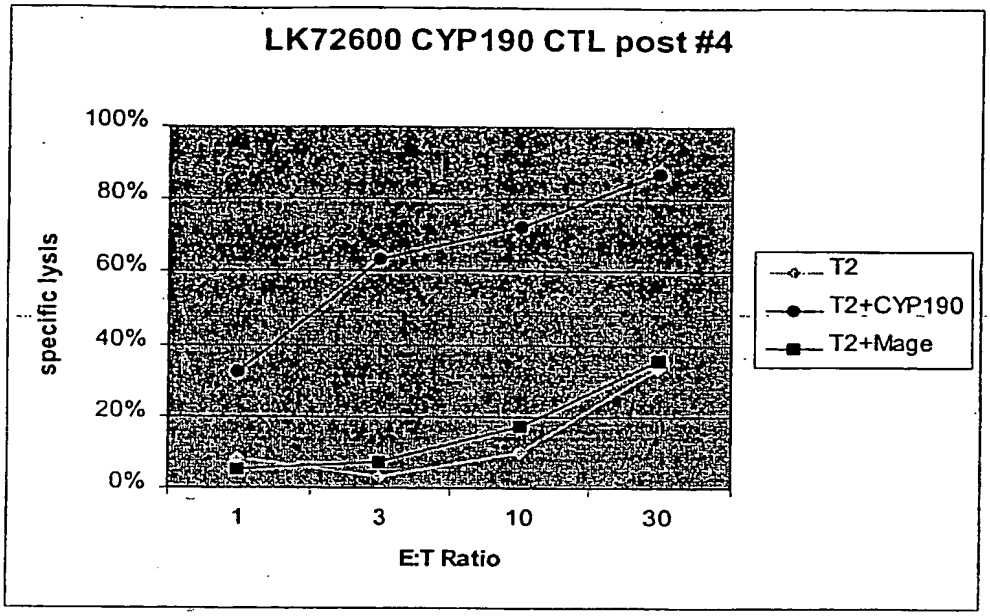


FIGURE 13B

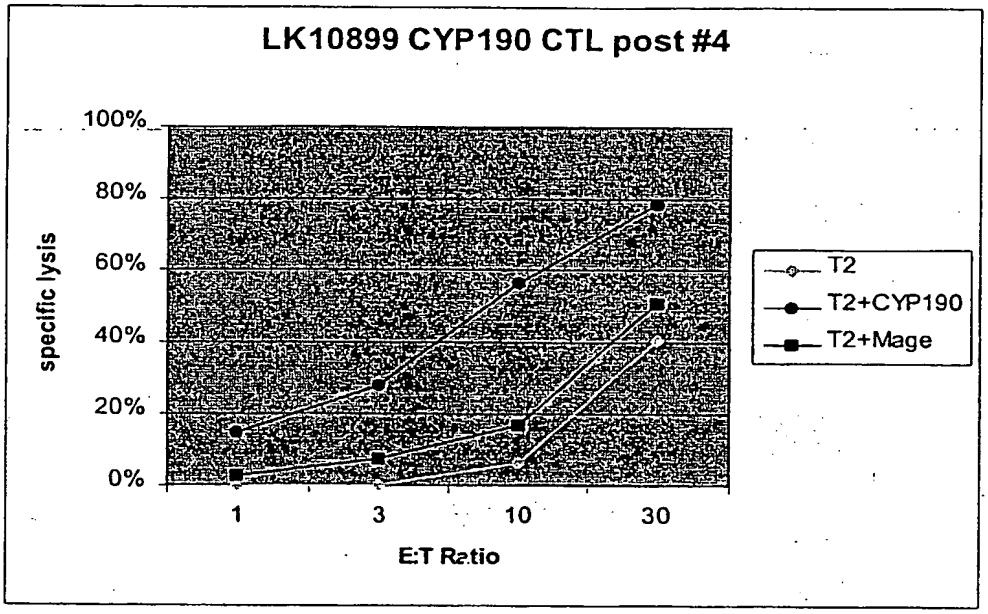


FIGURE 14

Generation and verification of CYP1B1specific tetramers

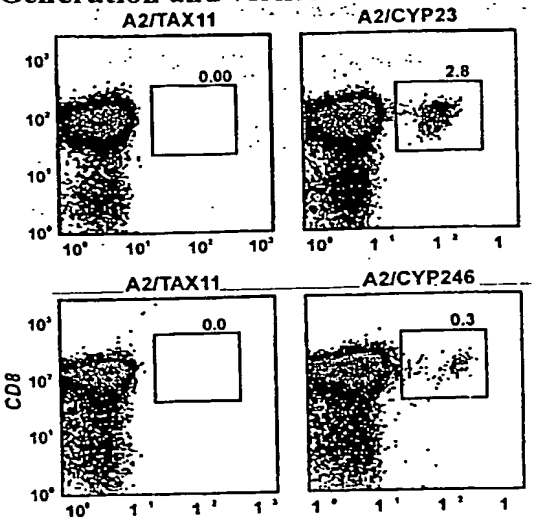


FIGURE 15

Analysis of MM pB samples

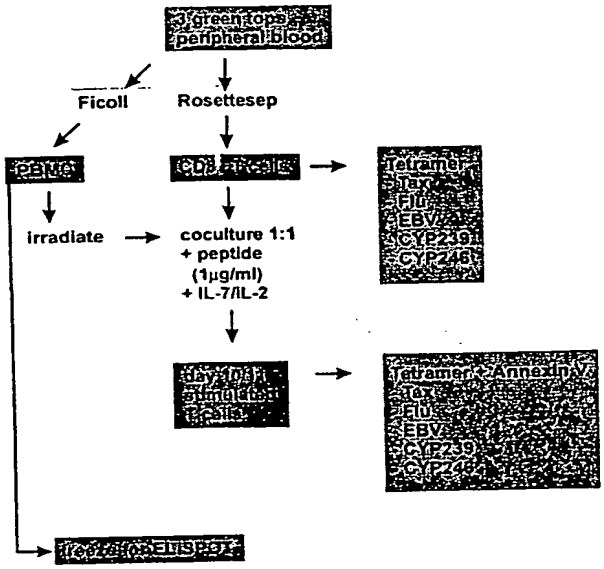
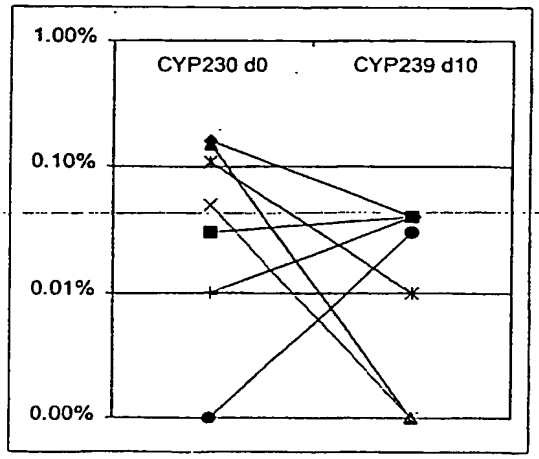


FIGURE 16

CYP239



CYP246

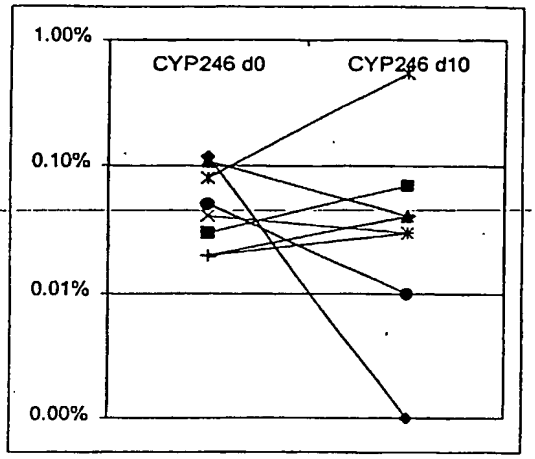
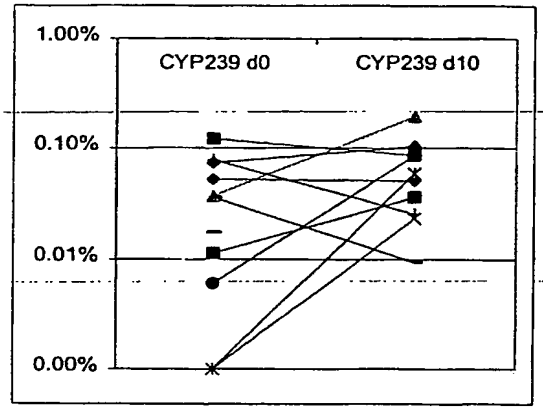
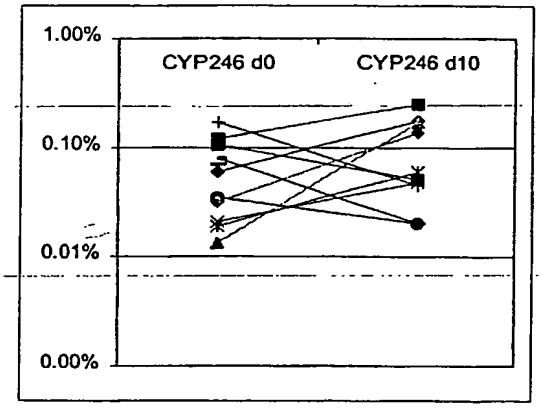


FIGURE 17

CYP239



CYP246



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(71) Applicants *(for all designated States except US)*: **DANA-FARBER CANCER INSTITUTE, INC.** [US/US]; 44 Binney Street, Boston, MA 02115 (US). **TRUSTEES OF BOSTON UNIVERSITY** [US/US]; 147 Bay State Road, Boston, MA 02215 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **SCHULTZE, Joachim, L.** [DE/US]; 37 Auburn Street, Brookline, MA 02146 (US). **VONDERHEIDE, Robert, H.** [DE/US]; Apartment 801, 1284 Beacon Street, Brookline, MA 02115 (US). **SHERR, David** [US/US]; 39 Hastings Street, West Roxbury, MA 02132 (US). **NADLER, Lee, M.** [US/US]; 36 Cross Hill Road, Newton, MA 02159 (US). **MAECKER, Britta** [DE/US]; 368 Longwood Avenue, #21, Boston, MA 02215 (US). **VON BERGWELT-BAILDON, Michael** [DE/US]; 24 A Prentiss Street, Cambridge, MA 02140 (US).

(74) Agent: **CLARK, Paul, T.**; Clark & Elbing LLP, 176 Federal Street, Boston, MA 02110-2214 (US).

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Published:
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10 January 2002

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 01/35810 A3

(54) Title: CANCER IMMUNOTHERAPY AND DIAGNOSIS USING CYTOCHROME P450 1B1

(57) Abstract: The invention provides methods for conducting cancer immunotherapy and diagnosis using cytochrome P450 1B1 and peptide fragments thereof.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/31513

A. CLASSIFICATION OF SUBJECT MATTER
IPC(7) : A01N 63/00; A61K 39/00; C12N 1/20, 15/85
US CL :424/93.21, 93.7, 184.1; 435/252.3, 325
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/93.21, 93.7, 184.1; 435/252.3, 325

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Please See Extra Sheet.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A, P	Database DERWENT, Accession No. 2000-365402, HAHN et al. Universal tumor-associated antigens such as telomerase catalytic subunit capable of binding major histocompatibility complex molecule useful for diagnosis, prevention and treatment of cancer. Abstract, WO 00/25813 A1 (DANA FARBER CANCER INSTITUTE, INC) 11 May 2000, see abstract	1-6, 19-23 and 28
A, P	Database CAPLUS on ACS, Accession No. 2000:494217, HEIDEL et al. Cytochrome P4501B1 mediates induction of bone marrow cytotoxicity and preleukemia cells in mice treated with 7,12-dimethylbenz[a]anthracene. Cancer Res. 2000. Vol. 60. No. 13, pages 3454-3460, see abstract.	1-6, 19-23 and 28

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search	Date of mailing of the international search report
13 APRIL 2001	14 JUN 2001

Name and mailing address of the ISA/US	Authorized officer
Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231	SUSAN UNGAR TERRY J. DEY PARALEGAL SPECIALIST TECHNOLOGY CENTER 1600
Facsimile No. (703) 305-3230	Telephone No. (703)

Form PCT/ISA/210 (second sheet) (July 1998) *

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/31513

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	Database CAPLUS on ACS, Accession No. 1999:203774, SPENCER et al. Quantitative analysis of constitutive and 2, 3, 7, 8-tetrachlorodibenzo-p-dioxin-induced cytochrome P450 1B1 expression in human lymphocytes. Cancer Epidemiology, Biomarkers Prev., 1999, Vol 8, No. 2 pages 139-146, see abstract	1-6, 19-23 and 28

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/31513

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Please See Extra Sheet.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1-6, 19-23 and 28

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/31513

B. FIELDS SEARCHED
Electronic data bases consulted (Name of data base and where practicable terms used):

PIR_66, BIOSIS, BIOTECHNO, CAPLUS, EMBASE, ESBIOBASE, GENBANK, LIFESCI, MEDLINE, SCISEARCH, TOXLINE, TOXLIT
search terms: 450 CYP1b1, gene, treat, antigen presenting cell, cytotoxic, T-lymphocyte

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING
This ISA found multiple inventions as follows:

This application contains the following inventions or groups of inventions which are not so linked as to form a single inventive concept under PCT Rule 13.1. In order for all inventions to be searched, the appropriate additional search fees must be paid.

Group I, claim(s) 1-6, and 19-23 and 28, drawn to a method of treating a patient with cytotoxic T cells and cytotoxic T cells.
Group II, claim(s) 7-10 and 19-23, drawn to a method of treating patients with an antigen presenting cell that activates cytotoxic T lymphocytes.
Group III, claim(s) 11-14 and 19-23, drawn to a method of treating a patient comprising administering a peptide of CYT p450 1B1.
Group IV, claim(s)15-18 and 19-23, drawn to a method of treating a patient comprising administering a nucleic acid encoding CYT P450 1B1 or a peptide thereof.
Group V, claim(s) 24-25, drawn to a method of assessing the level of immunity in a patient.
Group VI, claim(s) 26-27, drawn to drawn to a peptide.

Group VI, claim(s)29, drawn to an ex vivo generated antigen presenting cell.

This application contains claims directed to more than one species of the generic invention. These species are deemed to lack Unity of Invention because they are not so linked as to form a single inventive concept under PCT Rule 13.1. In order for more than one species to be searched, the appropriate additional search fees must be paid. The species are as follows:

The claims are deemed to correspond to the species listed above in the following manner:

The following claims are generic:
Group I, claim 1, the species are
Species (a) SEQ ID NO:1
Species (b) SEQ ID NO:2
Species (c) SEQ ID NO:3
Species (d) SEQ ID NO:4, all of claim 23

Group II, claim 1, the species are
Species (a) SEQ ID NO:1
Species (b) SEQ ID NO:2
Species (c) SEQ ID NO:3
Species (d) SEQ ID NO:4, all of claim 23

Group III, claim 1, the species are
Species (a) SEQ ID NO:1
Species (b) SEQ ID NO:2
Species (c) SEQ ID NO:3
Species (d) SEQ ID NO:4, all of claim 23

Group IV, claim 1, the species are
Species (a) SEQ ID NO:1
Species (b) SEQ ID NO:2
Species (c) SEQ ID NO:3
Species (d) SEQ ID NO:4, all of claim 23

Group VI, claim 1, the species are
Species (a) SEQ ID NO:1
Species (b) SEQ ID NO:2
Species (c) SEQ ID NO:3
Species (d) SEQ ID NO:4, all of claim 27

The inventions listed as Groups I-VI do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

The first invention claimed, claims 1-6, 20-23 and 28 is considered the main invention. If multiple products, processes of manufacture or uses are claimed, the first invention of the category first mentioned in the claims and the first recited invention of each of the other categories thereto will be considered as the main invention of the claims, see PCT Article 17(3)(a) and 1.476(c). After that, all other products and methods will be broken out as separate groups. (See 37 CFR 1.475(d). All of the other groups are drawn to products of methods not recited in the main invention.

The species listed above do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, the species lack the same or corresponding special technical features for the following reasons:

The species recited relate to products with different sequences and therefore different structures and functions.